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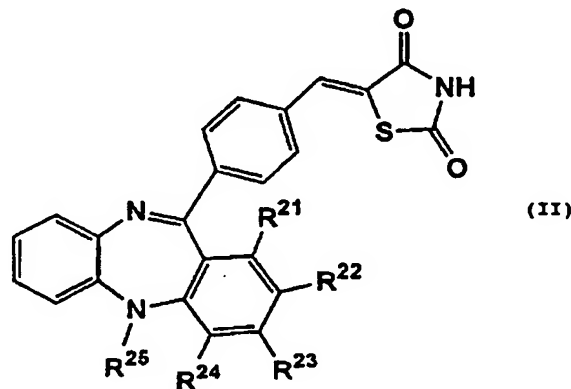
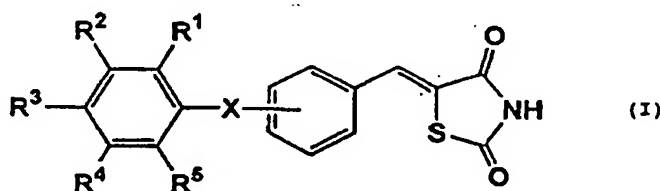
<p>(51) 国際特許分類6 C07D 277/34, 417/10, A61K 31/425, 31/55</p>	<p>A1</p>	<p>(11) 国際公開番号 WO99/24415</p> <p>(43) 国際公開日 1999年5月20日 (20.05.99)</p>
<p>(21) 国際出願番号 PCT/JP98/05091</p> <p>(22) 国際出願日 1998年11月12日 (12.11.98)</p> <p>(30) 優先権データ 特願平9/310835 1997年11月12日 (12.11.97) JP</p> <p>(71) 出願人 (米国を除くすべての指定国について) 株式会社 医薬分子設計研究所 (INSTITUTE OF MEDICINAL MOLECULAR DESIGN, INC.) [JP/JP] 〒113-0033 東京都文京区本郷5丁目24番5号 角川本郷ビル4F Tokyo, (JP)</p> <p>(71) 出願人 ; および</p> <p>(72) 発明者 影近弘之 (KAGECHIKA, Hiroyuki) [JP/JP] 〒178-0062 東京都練馬区大泉町2-39-6 Tokyo, (JP)</p> <p>(72) 発明者 ; および</p> <p>(75) 発明者 / 出願人 (米国についてののみ) 橋本祐一 (HASHIMOTO, Yuichi) [JP/JP] 〒161-0032 東京都新宿区中落合3丁目16番18号 Tokyo, (JP)</p> <p>板井昭子 (ITAI, Akiko) [JP/JP] 〒113-0033 東京都文京区本郷5-16-6 Tokyo, (JP)</p>	<p>(74) 代理人 弁理士 今村正純, 外 (IMAMURA, Masazumi et al.) 〒104-0031 東京都中央区京橋1丁目5番5号 KRFビル5階 Tokyo, (JP)</p> <p>(81) 指定国 AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO特許 (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), ユーラシ ア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), 欧州特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>添付公開書類 国際調査報告書</p>	

(54) Title: RETINOID RECEPTOR AGONISTS

(54) 発明の名称 レチノイドレセプター作用剤

(57) Abstract

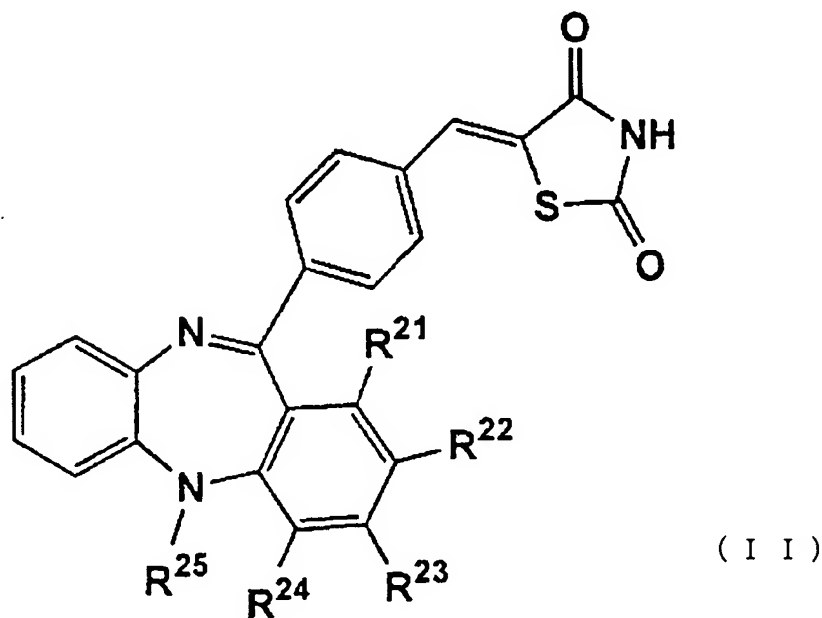
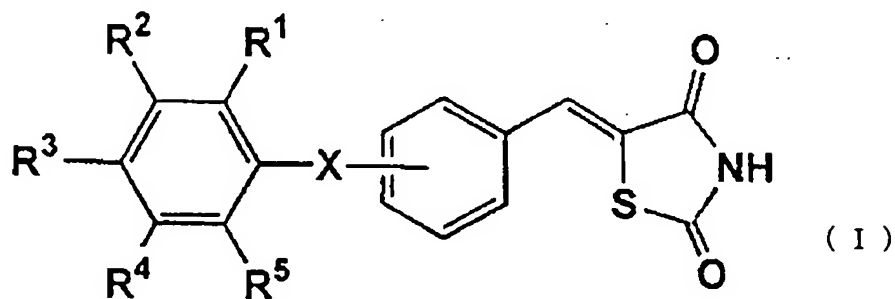
Retinoid receptor agonists having retinoic effects or regulatory effects of increasing or suppressing retinoid actions. The agonists include compounds represented by general formulas (I) and (II).



## (57)要約

レチノイン様作用、又はレチノイドの作用に対して増強若しくは抑制などの調節作用を有するレチノイドレセプター作用性物質を提供する。

上記物質として、下記の一般式(I)及び一般式(II)で表される化合物が挙げられる。



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## 明 細 書

## レチノイドレセプター作用剤

## 技術分野

本発明は、レチノイン酸などのレチノイドと同様な生理活性又はレチノイドの作用を調節する作用を有するレチノイドレセプター作用性物質、及び該化合物を有効成分として含む医薬の発明に関するものである。

## 背景技術

レチノイン酸（ビタミンA酸）はビタミンAの活性代謝産物であり、発生途上にある未熟な細胞を特有な機能を有する成熟細胞へと分化させる作用や、細胞の増殖促進作用や生命維持作用などの極めて重要な生理作用を有している。これまでに合成された種々のビタミンA誘導体、例えば、特開昭 61-22047 号公報や特開昭 61-76440 号公報記載の安息香酸誘導体、及びジャーナル・オブ・メディシナル・ケミストリー（Journal of Medicinal Chemistry, 1988, Vol. 31, No. 11, p. 2182）に記載の化合物なども、同様な生理作用を有することが明らかにされている。レチノイン酸及びレチノイン酸様の生物活性を有する上記化合物は「レチノイド」と総称されている。

例えば、オール・トランス(all-trans)・レチノイン酸は、細胞核内に存在する核内レセプター・スーパーファミリー (Evans, R. M., Science, 240, p. 889, 1988) に属するレチノイン酸レセプター (RAR) にリガンドとして結合して、動物細胞の増殖・分化あるいは細胞死などを制御することが明らかにされている (Petkovich, M., et al., Nature, 330, pp. 444-450, 1987)。レチノイン酸様の生物活性を有する上記化合物（例えば、4-[(5, 6, 7, 8-tetrahydro-5, 5, 8, 8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid: Am80 など）も、レチノイン酸と同様に RAR に結合して生理活性を発揮することが示唆されている

(Hashimoto, Y., Cell struct. Funct., 16, pp.113-123, 1991; Hashimoto, Y., et al., Biochem. Biophys. Res. Commun., 166, pp.1300-1307, 1990 を参照)。

これらの化合物は、臨床的には、ビタミンA欠乏症、上皮組織の角化症、リウマチ、遅延型アレルギー、骨疾患、及び白血病やある種の癌の治療や予防に有用であることが見出されている。しかしながら、これらのレチノイドは多様な生物活性を有しているがゆえに、副作用の観点からは必ずしも満足すべき医薬とはいえない。従って、特徴的な作用を有するレチノイドやその制御分子の創製が切望されていた。

レチノイドの作用調節剤としては、4-[5H-2,3-(2,5-ジメチル-2,5-ヘキサノ)-5-メチルジベンゾ[b,e][1,4]ジアゼピン-11-イル]安息香酸や4-[1,3-ジヒドロ-7,8-(2,5-ジメチル-2,5-ヘキサノ)-2-オキソ-2H-1,4-ベンゾジアゼピン-5-イル]-安息香酸などのベンゾジアゼピン誘導体が知られている(PCT/JP96/2709, 国際公開 W097/11061)。これらの化合物は、それ自体はレチノイド作用を有しないか、あるいはそのレチノイド作用が微弱であるにもかかわらず、レチノイン酸などのレチノイドの作用を顕著に増強する作用を有しており、ビタミンA欠乏症、上皮組織の角化症、リウマチ、遅延性アレルギー、骨疾患、又は白血病やある種の癌の治療や予防に有用であることが示唆されている。

レチノイン酸の生理活性の発現については、レチノイド X レセプター(RXR, 9-cis-レチノイン酸をリガンドとする)の存在が証明されている。レチノイド X レセプターは、レチノイン酸レセプター(RAR)と二量体を形成し、遺伝子の転写を惹起ないし抑制して、レチノイン酸の生理活性の発現を調節していることが明らかにされた(Mangelsdorf, D.J. et al., Nature, 345, pp.224-229)。レチノイド X レセプター(RXR)は、レチノイン酸レセプター(RAR)のほか、活性ビタミン D<sub>3</sub>の核内レセプターや、脂肪代謝に関与するといわれる PPAR 及びその他のレセプター類に対して結合して、これらのレセプターに結合するビタミン D<sub>3</sub>やチロキシンなどの生理活性物質の作用の発現を制御することが明らかにされている(Mangelsdorf, D.J. et al., The Retinoids, 2nd Ed., Ravan Press,

pp. 319-350, 1994)。

また、レチノイド作用調節剤として、レチノイドに対して拮抗的に作用し、上記レチノイドの代表的な作用を減弱する化合物の存在も知られている (Eyrolles, L., et al., Journal of Medicinal Chemistry, 37(10), pp. 1508-1517, 1994)。この刊行物には、例えば、4-(5H-7, 8, 9, 10- テトラヒドロ-5, 7, 7, 10, 10- ペンタメチルベンゾ[e] ナフト[2, 3-b][1, 4] ジアゼピン-13-イル) 安息香酸などの化合物がレチノイドのアンタゴニストとして作用することが開示されている。また、本発明者により、4-(13H-10, 11, 12, 13- テトラヒドロ-10, 10, 13, 13, 15-ペンタメチルジナフト[2, 3-b][1, 2-e][1, 4] ジアゼピン-7- イル) 安息香酸などの化合物が、レチノイド・アンタゴニストとして見い出されている (特願平 7-255912 号明細書)。

一方、レチノイン酸や Am80 などのレチノイドのカルボキシル基、あるいは上記のレチノイド作用増強性化合物やレチノイドアンタゴニストのカルボキシル基は、従来、それぞれ所望の生物活性に必須の官能基であると考えられており、例えば、スルホンアミドやテトラゾールなどの官能基で置換すると所望の生物活性が失われることが知られている。チアゾリジン骨格を有するジグリタゾンやトログリタゾンなどの化合物が、核内レセプタースーパーファミリーに属する PPAR (peroxisome proliferator-activated receptor) の $\gamma$ サブタイプに作用することが示唆されてはいるが、上記の生理活性化合物のカルボキシル基をチアゾリジン環で置き換えた化合物がレチノイドレセプターに相互作用して生理活性を発揮することは従来全く知られていない。

チアゾリジンジオン誘導体として、血糖低下作用を有する N-ベンジル型の 2, 4-チアゾリジンジオン誘導体が知られている (特開平 9-48771 号公報、及び第 17 回メディシナルケミストリーシンポジウム・第 6 回医薬化学部会年会公演要旨集、第 114 ~115 頁、1-P-30、1997 年 10 月 27 日、日本薬学会発行)。しかしながら、上記刊行物には、これらのチアゾリジンジオン誘導体がレチノイド様作用を有すること、あるいはレチノイド作用調節剤として機能することについては全く示唆

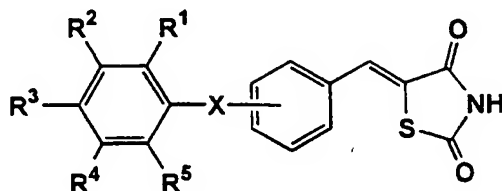
ないし教示がない。

#### 発明の開示

本発明の課題は、レチノイン様作用、又はレチノイドの作用に対して調節作用（例えばレチノイドの作用を増強又は抑制する作用）を有するレチノイドレセプター作用性物質を提供することにある。本発明の別の課題は、上記の化合物を有効成分として含む医薬を提供することにある。

本発明者は上記の課題を解決すべく鋭意努力した結果、下記的一般式で示されるチアゾリジン化合物がレチノイン酸様の生物作用を有しており、あるいはレチノイドの作用を増強又は抑制する作用を有することを見いだした。本発明は上記の知見を基にして完成されたものである。

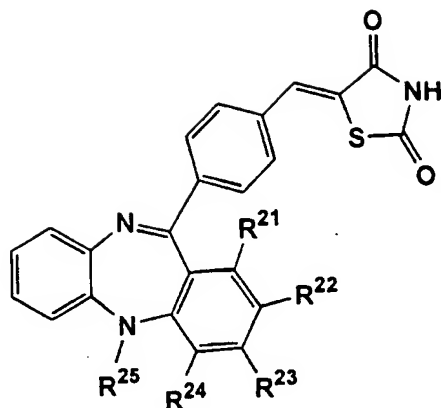
すなわち本発明は、下記的一般式(I)：



〔式中、R<sup>1</sup>、R<sup>2</sup>、R<sup>3</sup>、R<sup>4</sup>、及び R<sup>5</sup> はそれぞれ独立に水素原子又は低級アルキル基を示し、それらのうちの隣接する2つの基は一緒になってそれらが結合するフェニル環上の炭素原子とともに1又は2以上のアルキル基を有することもある5員環又は6員環を形成してもよく；X は-C(R<sup>6</sup>)=CH-、-CH=C(R<sup>7</sup>)-、-N(R<sup>8</sup>)-CO-、-CO-N(R<sup>9</sup>)-、-C(=CHR<sup>10</sup>)-、-CO-、又は -NR<sup>11</sup>- で表される基（式中、R<sup>6</sup>、R<sup>7</sup>、R<sup>8</sup>、R<sup>9</sup>、R<sup>10</sup>、及び R<sup>11</sup> はそれぞれ独立に水素原子又は低級アルキル基を示す）を示す〕

で表される化合物、若しくは

下記的一般式(II)：



〔式中、 $R^{21}$ 、 $R^{22}$ 、 $R^{23}$ 、及び  $R^{24}$  はそれぞれ独立に水素原子又は低級アルキル基を示し、それらのうちの隣接する2つの基は一緒になってそれらが結合するフェニル環上の炭素原子とともに1又は2以上のアルキル基を有することもある5員環又は6員環を形成してもよく； $R^{25}$  は水素原子又は低級アルキル基を示す〕で表される化合物、又はそれらの塩を提供するものである。

別の観点からは、上記一般式で表される化合物及び生理学的に許容されるそれらの塩、並びにそれらの水和物及び溶媒和物を有効成分として含む医薬が提供される。この医薬は、レチノイド様作用剤又はレチノイド作用調節剤（好ましくはレチノイド作用増強剤又はレチノイド作用抑制剤）として有用である。

別の観点からは、上記の医薬の製造のための上記物質の使用；並びに核内レセプター・スーパーファミリー（Evans, R.M., Science, 240, p. 889, 1988）に属するレセプター、好ましくはレチノイドレセプター（RAR 及び／又は RXR）の関与する疾患の予防及び／又は治療方法であって、上記物質の有効量をヒトを含む哺乳類動物に投与する工程を含む方法が提供される。

#### 発明を実施するための最良の形態

上記一般式(I)において、 $R^1$ 、 $R^2$ 、 $R^3$ 、 $R^4$ 、及び  $R^5$  はそれぞれ独立に水素原子又は低級アルキル基を示す。低級アルキル基としては、炭素数1ないし6個程度、好ましくは炭素数1ないし4個の直鎖又は分枝鎖のアルキル基を用いることがで

きる。例えば、メチル基、エチル基、*n*-プロピル基、イソプロピル基、*n*-ブチル基、*sec*-ブチル基、又は *tert*-ブチル基などを用いることができる。

また、 $R^1$ 、 $R^2$ 、 $R^3$ 、 $R^4$ 、及び  $R^5$  からなる群から選ばれる隣接する2つの基が一緒になって、それらが結合するフェニル環上の炭素原子とともに1又は2以上のアルキル基を有することもある5員環又は6員環を1個又は2個、好ましくは1個形成してもよい。環上に置換可能なアルキル基としては、炭素数1ないし6個程度、好ましくは炭素数1ないし4個の直鎖又は分枝鎖のアルキル基を用いることができる。例えば、メチル基、エチル基などを用いることができ、好ましくは2～4個のメチル基、さらに好ましくは4個のメチル基が置換していてもよい。例えば、 $R^2$  及び  $R^3$  が置換するフェニル環と  $R^2$  及び  $R^3$  とにより、5,6,7,8-テトラヒドロナフタレン環や 5,5,8,8-テトラメチル-5,6,7,8-テトラヒドロナフタレン環などが形成されることが好ましい。

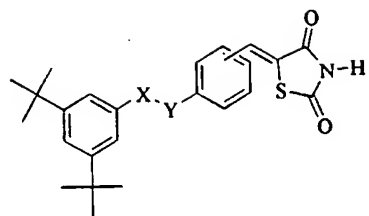
X は  $-C(R^6)=CH-$ 、 $-CH=C(R^7)-$ 、 $-N(R^8)-CO-$ 、 $-CO-N(R^9)-$ 、 $-C(=CHR^{10})-$ 、 $-CO-$ 、又は  $-NR^{11}-$  で表される基のいずれかを示す。これらの基において、 $R^6$ 、 $R^7$ 、 $R^8$ 、 $R^9$ 、 $R^{10}$ 、及び  $R^{11}$  はそれぞれ独立に水素原子又は低級アルキル基を示すが、低級アルキル基としては、例えば炭素数1ないし4個の直鎖又は分枝鎖のアルキル基を用いることができる。より具体的には、メチル基、エチル基などを用いることが好ましい。ベンジリデンチアゾリジンジオン部分のフェニル基上における X の置換位置は特に限定されないが、メタ置換又はパラ置換であることが好ましい。

上記一般式(II)において、 $R^{21}$ 、 $R^{22}$ 、 $R^{23}$ 、及び  $R^{24}$  はそれぞれ独立に水素原子又は低級アルキル基を示す。低級アルキル基としては、炭素数1ないし6個程度、好ましくは炭素数1ないし4個の直鎖又は分枝鎖のアルキル基を用いることができる。例えば、メチル基、エチル基、*n*-プロピル基、イソプロピル基、*n*-ブチル基、*sec*-ブチル基、又は *tert*-ブチル基などを用いることができる。 $R^{25}$  は水素原子又は低級アルキル基を示すが、低級アルキル基としては、例えば炭素数1ないし4個の直鎖又は分枝鎖のアルキル基を用いることができる。より具体的には、メチル基、エチル基などを用いることが好ましい。

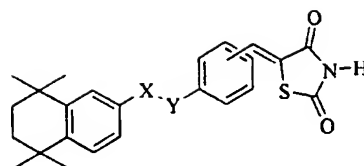
また、 $R^{21}$ 、 $R^{22}$ 、 $R^{23}$ 、及び  $R^{24}$  からなる群から選ばれる隣接する2つの基が一緒になって、それらが結合するフェニル環上の炭素原子とともに1又は2以上のアルキル基を有することもある5員環又は6員環を1個又は2個、好ましくは1個形成してもよい。環上に置換可能なアルキル基としては、炭素数1ないし6個程度、好ましくは炭素数1ないし4個の直鎖又は分枝鎖のアルキル基を用いることができる。例えば、メチル基、エチル基などを用いることができ、好ましくは2～4個のメチル基、さらに好ましくは4個のメチル基が置換していてもよい。例えば、 $R^{22}$  及び  $R^{23}$  が置換するフェニル環と  $R^{22}$  及び  $R^{23}$  とにより、5,6,7,8-テトラヒドロナフタレン環や5,5,8,8-テトラメチル-5,6,7,8-テトラヒドロナフタレン環などが形成されることが好ましい。

上記化合物は塩基付加塩を形成する場合があります、例えば、ナトリウム塩、カリウム塩、マグネシウム塩、若しくはカルシウム塩などの金属塩、アンモニウム塩、又はトリエチルアミン塩若しくはエタノールアミン塩などの有機アミン塩などとして存在することがあるが、このような塩のうち、生理学的に許容される塩を本発明の医薬の有効成分として用いることができる。また、上記化合物は、置換基の種類に応じて1個または2個以上の不斉炭素を有する場合がありますが、これらの不斉炭素に基づく任意の光学異性体、光学異性体の任意の混合物、ラセミ体、2個以上の不斉炭素に基づくジアステレオ異性体、ジアステレオ異性体の任意の混合物などは、いずれも本発明の範囲に包含される。さらに、二重結合のシス又はトランス結合に基づく幾何異性体、及び幾何異性体の任意の混合物や、遊離化合物又は塩の形態の化合物の任意の水和物又は溶媒和物も本発明の範囲に包含される。

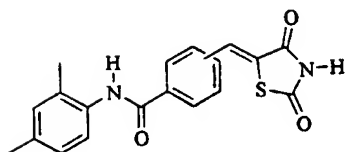
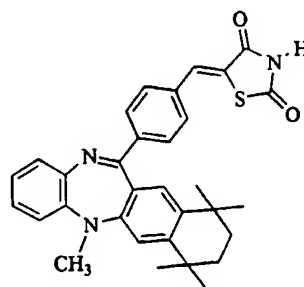
本発明の化合物のうち、好ましい化合物として以下の化合物を挙げることができるが、本発明の化合物、又は本発明の医薬の有効成分として利用可能な化合物は下記の化合物に限定されることはない（下記の説明において、para 及び meta はそれぞれベンジリデンチアゾリジンジオン部分のフェニル基上における X の置換位置がパラ位及びメタ位であることを示し、Me はメチル基を示す）。



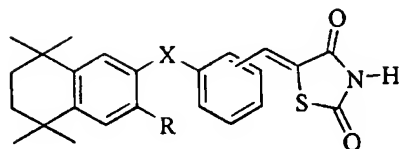
	X	Y	thiazolidine
TZ151	C=O	NH	para
TZ153	C=O	NH	meta
TZ155	NH	C=O	para
TZ157	NH	C=O	meta
TZ161	C=O	NMe	para
TZ163	C=O	NMe	meta
TZ165	NMe	C=O	para
TZ167	NMe	C=O	meta



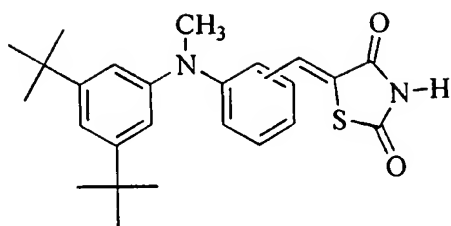
	X	Y	thiazolidine
TZ181	C=O	NH	para
TZ183	C=O	NH	meta
TZ185	NH	C=O	para
TZ187	NH	C=O	meta
TZ191	C=O	NMe	para
TZ193	C=O	NMe	meta
TZ195	NMe	C=O	para
TZ197	NMe	C=O	meta

TZ175  
TZ177thiazolidine  
para  
meta

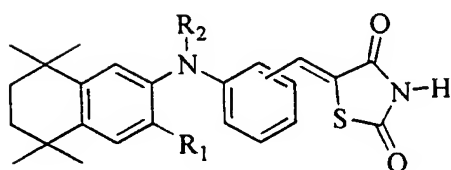
TZ201



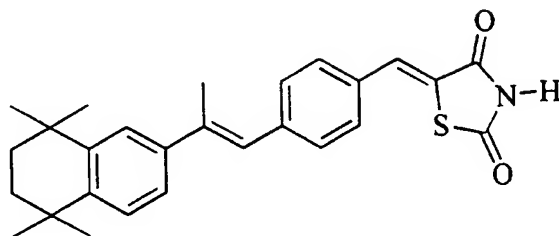
	X	R	thiazolidine
TZ221	C=O	H	para
TZ223	C=O	H	meta
TZ225	C=O	Me	para
TZ227	C=O	Me	meta
TZ241	C=C	H	para
TZ243	C=C	H	meta
TZ245	C=C	Me	para
TZ247	C=C	Me	meta



thiazolidine  
TZ315 para  
TZ317 meta



	R <sub>1</sub>	R <sub>2</sub>	thiazolidine
TZ321	H	H	para
TZ323	H	H	meta
TZ325	H	Me	para
TZ327	H	Me	meta
TZ331	Me	H	para
TZ333	Me	H	meta
TZ335	Me	Me	para
TZ337	Me	Me	meta



TZ91

上記の式(I) 及び式(II)の化合物の製造方法については、上記の代表的な化合物についての合成例が本明細書の実施例に具体的かつ詳細に示されている。従って、これらの実施例を参照することにより、また、必要に応じてこれらの方法に適宜の改変や修飾を加えることにより、上記一般式(I) 又は(II)で示される本発明の化合物に包含される任意の化合物を当業者は容易に製造することが可能である。

上記の式(I) 及び式(II)の化合物は、レチノイドレセプター（本明細書におい

て用いられる「レチノイドレセプター」という用語は、レチノイン酸レセプター RAR 及び RXR を包含しており、レチノイン酸などのレチノイドが相互作用可能なレセプターの 1 種又は 2 種以上を意味している。) に対して相互作用することができ、それ自体がアゴニストとしてレチノイド様の生理活性を発揮するか、あるいはレチノイドの生理活性を増強又は抑制する作用を有している。

従って、上記化合物を有効成分として含む医薬は、レチノイド様作用剤又はレチノイド作用調節剤として有用である。上記の式(I) 及び式(II)の化合物の上記のいずれの作用を有しているかは、本明細書の実施例に詳細に記載された方法に従って容易に確認することができる。また、レチノイド作用増強性の化合物の評価方法については国際公開 W097/11061 (PCT/JP96/2709) に記載があり、レチノイドの作用抑制性の化合物の評価方法については Eyrolles, L., et al., Journal of Medicinal Chemistry, 37(10), pp.1508-1517, 1994、及び特願平 7-255912 号明細書に記載がある。

上記の化合物のうち、レチノイド様作用を有する化合物は、例えば、細胞分化作用、細胞増殖促進作用、及び生命維持作用などを有しており、ビタミン A 欠乏症、上皮組織の角化症、乾癬、アレルギー疾患、リウマチなどの免疫性疾患、骨疾患、白血病、又は癌の予防・治療のための医薬の有効成分として用いることができる。

また、上記の化合物のうち、レチノイド作用増強性の化合物は、それ自体はレチノイド様の作用を実質的に有していないか、あるいは微弱又は中程度のレチノイド様作用を有するが、該化合物をレチノイン酸などのレチノイドと共存させた場合には、レチノイドの生理活性(代表的なものとして細胞分化作用、細胞増殖促進作用、及び生命維持作用など)が顕著に増強される。

いかなる特定の理論に拘泥するわけではないが、このようなレチノイド作用増強性の化合物自体がレチノイド作用を有する場合には、その作用は相乗的作用である。従って、レチノイド作用増強性の化合物は、レチノイン酸やレチノイン酸様の生物活性を有する上記化合物(例えば、4-[(5,6,7,8-tetrahydro-5,5,8,8-

tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid: Am80 など) などのレチノイドをビタミンA欠乏症、上皮組織の角化症、乾癬、アレルギー疾患、リウマチなどの免疫性疾患、骨疾患、白血病、又は癌の予防・治療のための医薬として投与する場合に、該レチノイドの作用増強剤として用いることができる。

また、上記のレチノイド作用増強性の化合物は、レチノイドを上記疾患の治療・予防のために投与しない場合においても、生体内に既に存在するレチノイン酸の作用を増強するので、上記疾患の治療・予防の目的で上記化合物を医薬として投与することも可能である。さらに、この化合物は、レチノイドに対しての作用増強効果のみならず、細胞の核内に存在する核内レセプター・スーパーファミリー (Evans, R. M., Science, 240, p. 889, 1988) に属するレセプターに結合して生理作用を発揮するステロイド化合物、ビタミン D<sub>3</sub> などのビタミンD化合物、又はチロキシンの生理活性物質の作用増強剤として用いることもできる。例えば、糖尿病、動脈硬化症、高脂血症、高コレステロール血症、骨疾患、リウマチ、又は免疫性疾患などの疾患の予防及び／又は治療のための医薬として有用である。

このような核内レセプターとして、例えば、活性ビタミン D<sub>3</sub> の核内レセプター、脂肪代謝に関与する PPAR、チロキシンのレセプター、及び COUP などが知られているが (以上のレセプターについて、Mangelsdorf, D. J. et al., The Retinoids, 2nd Ed., Raven Press, pp. 319-350, 1994 を参照のこと)、これらのレセプターは、いずれもレチノイド X レセプター (RXR) に結合して上記生理活性物質の作用を発現させることが明らかにされている。

上記の化合物のうち、レチノイド作用抑制性の化合物は、レチノイドの生理活性 (代表的なものとして細胞分化作用、細胞増殖促進作用、及び生命維持作用など) を顕著に抑制する作用を有している。いかなる特定の理論に拘泥するわけではないが、このような作用を有する化合物は、レチノイン酸レセプター (RAR) とともに二量体を形成するレチノイド X レセプター (RXR) に結合し、レチノイン酸などのレチノイドの生理活性の発現を調節するものと考えられる。この化合物は、生体中のビタミンAの過剰による内因的なビタミンA過剰症、あるいは、ビ

タミンA欠乏症、上皮組織の角化症、乾癬、アレルギー疾患、リウマチなどの免疫性疾患、骨疾患、白血病、又は癌の予防・治療のために投与されるレチノイン酸やレチノイン酸様の生物活性を有する化合物（例えば、4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid: Am80 など）により惹起される外因的なビタミンA過剰症の治療及び／又は予防に有用である。

レチノイド作用抑制性の化合物はそれ自体を単独で、又は他のレチノイドや制ガン剤と組み合わせて投与することにより、白血病などの癌を治療することが可能である。さらに、上記の化合物は、細胞の核内に存在する核内レセプター・スーパーファミリー (Evans, R. M., Science, 240, p. 889, 1988) に属するレセプターに結合して生理活性を発現する物質、例えば、ステロイド化合物、ビタミンD<sub>3</sub>などのビタミンD化合物、又はチロキシンやリガンド不明のオーファンレセプターなどの作用を抑制することができるので、これらの物質の生理活性発現の調節に用いることもできる。従って、レチノイド X レセプター (RXR) に結合するレチノイド作用抑制性の化合物は、例えば、核内レセプター・スーパーファミリーに属する核内レセプターの1又は2以上が関与する生物作用の異常を伴う疾患の予防及び／又は治療に用いることができる。

本発明の医薬は、上記の式(I)で表される化合物及びその塩、並びにそれらの水和物及び溶媒和物からなる群から選ばれる物質、あるいは上記の式(II)で表される化合物及びその塩、並びにそれらの水和物及び溶媒和物からなる群から選ばれる物質の1種または2種以上を有効成分として含んでいる。本発明の医薬としては上記物質それ自体を投与してもよいが、好ましくは、当業者に周知の方法によって製造可能な経口用あるいは非経口用の医薬組成物として投与することができる。経口投与に適する医薬用組成物としては、例えば、錠剤、カプセル剤、散剤、細粒剤、顆粒剤、液剤、及びシロップ剤等を挙げることができ、非経口投与に適する医薬組成物としては、例えば、注射剤、坐剤、吸入剤、点眼剤、点鼻剤、軟膏剤、クリーム剤、及び貼付剤等を挙げることができる。

上記の医薬組成物は、薬理学的、製剤学的に許容しうる添加物を加えて製造することができる。薬理学的、製剤学的に許容しうる添加物の例としては、例えば、賦形剤、崩壊剤ないし崩壊補助剤、結合剤、滑沢剤、コーティング剤、色素、希釈剤、基剤、溶解剤ないし溶解補助剤、等張化剤、pH 調節剤、安定化剤、噴射剤、及び粘着剤等を挙げることができる。

本発明の医薬の投与量は特に限定されず、その作用の種類や作用の強弱などに応じて適宜選択することができ、さらに患者の体重や年齢、疾患の種類や症状、投与経路など通常考慮すべき種々の要因に応じて、適宜増減することができる。一般的には、レチノイド様作用を有する化合物を有効成分として含む医薬については、レチノイン酸などを医薬として用いる場合の投与量に準じて、またはその投与量を参考にして適宜選択することが可能である。例えば、経口投与の場合には成人一日あたり 0.01 ～1,000 mg 程度の範囲で用いることができる。また、レチノイド作用増強性又はレチノイド作用抑制性の化合物を有効成分として含む医薬についても同様に投与量を選択することが可能であり、例えば、経口投与の場合には成人一日あたり 0.01 ～1,000 mg 程度の範囲で用いることができる。

#### 実施例

以下、本発明を実施例によりさらに具体的に説明するが、本発明の範囲は下記の実施例の範囲に限定されることはない。なお、実施例中の化合物番号は、上記に好ましい例として具体的に示した化合物及び下記の合成スキーム中の番号に対応している。

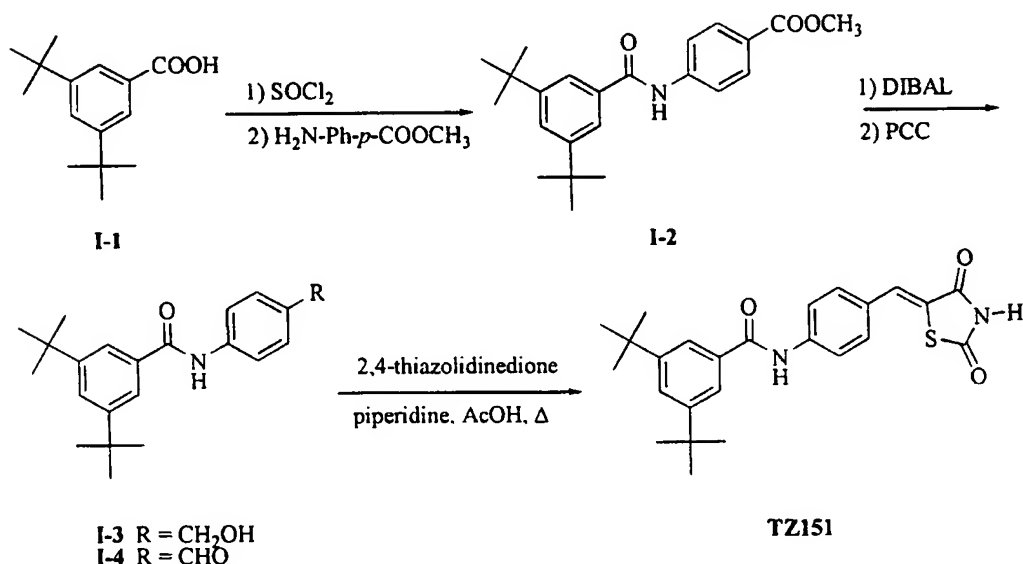
#### 例 1 : TZ91 の合成

4-[2-(5,6,7,8-テトラメチル-5,5,8,8- テトラヒドロ-2- ナフチル) プロペニル] ベンズアルデヒド 24 mg (0.072 mmol) 、2,4-チアゾリジンジオン 10 mg (0.085 mmol) およびピペリジン 5 mg (0.058 mmol) をエタノール 2.5 ml に溶かし、一晚還流した。反応液を 1 N 塩酸にあげ、酢酸エチルで抽出した。有機

層を水で洗い、 $\text{Na}_2\text{SO}_4$  で脱水、溶媒留去の後、メタノールより再結晶して TZ91 (定量的) を得た。

TZ91: Yellow needles (メタノール); mp 227–229 °C;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 8.24 (br s, 1 H), 7.87 (s, 1 H), 7.51 (d, 2 H,  $J = 8.8$  Hz), 7.48 (d, 2H,  $J = 8.8$  Hz), 7.45 (d, 1 H,  $J = 1.5$  Hz), 7.33 (d, 1 H,  $J = 8.4$  Hz), 7.30 (dd, 1 H,  $J = 8.4, 1.8$  Hz), 6.78 (br s, 1 H), 2.32 (d, 3 H,  $J = 1.5$  Hz), 1.71 (s, 4 H), 1.34 (s, 6 H), 1.31 (s, 6 H); Anal. Calcd. for  $\text{C}_{27}\text{H}_{29}\text{NO}_2\text{S}$ , C: 75.15 %, H: 6.77 %, N: 3.25 %; Found C: 75.08 %, H: 6.97 %, N: 3.11 %.

## 例 2 : TZ151 の合成



3,5-ジ-tert-ブチル安息香酸 (I-1) 1.00 g (4.27 mmol) をチオニルクロライド 2.50 g (21.0 mmol)、無水ベンゼン 12 ml に懸濁し、14 時間還流した。チオニルクロライドを留去し、p-アミノ安息香酸メチル 645 mg (4.27 mmol) を加え、無水ベンゼン 30 ml、無水ピリジン 1 ml に懸濁し、室温で 1.5 時間攪拌した。反応液に氷水、2 N 塩酸を加え、酢酸エチルで抽出した。有機層を食塩水

で洗い、 $\text{MgSO}_4$  で脱水し、濃縮した。シリカゲルカラムクロマトグラフィー（塩化メチレン）で精製して、化合物 I-2 を 1.03 g (66 %) 得た。

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 8.06 (d, 2 H,  $J = 8.8$  Hz), 7.90 (br s, 1 H), 7.75 (d, 2 H,  $J = 8.8$  Hz), 7.66 (d, 2 H,  $J = 1.5$  Hz), 7.64 (t, 1 H,  $J = 1.8$  Hz), 3.92 (s, 3 H), 1.37 (s, 18 H).

化合物 I-2 1.02 g (2.78 mmol) を THF 30 ml に溶かし、 $-20^\circ\text{C}$  にて DIBAL 8.34 ml (1 M トルエン溶液、8.34 mmol) を徐々に加えた。30 分後、反応液を 2 N 塩酸に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、 $\text{MgSO}_4$  で脱水、溶媒を濃縮した。残渣をシリカゲルカラムクロマトグラフィー（酢酸エチル： $n$ -ヘキサン = 1 : 1）で精製して、化合物 I-3 を 786 mg (83 %) 得た。

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 7.78 (br s, 1 H), 7.67 (d, 2 H,  $J = 1.8$  Hz), 7.65 (d, 2 H,  $J = 8.8$  Hz), 7.62 (t, 1 H,  $J = 1.8$  Hz), 7.38 (d, 2 H,  $J = 8.8$  Hz), 4.69 (d, 2 H,  $J = 5.9$  Hz), 1.37 (s, 18 H).

化合物 I-3 780 mg (2.30 mmol) をメタノールフリー塩化メチレン 22 ml に溶かし、PCC 992 mg (4.60 mmol) を加え、室温で 2.5 時間攪拌した。反応液を濃縮し、シリカゲルカラムクロマトグラフィー（酢酸エチル： $n$ -ヘキサン = 1 : 4）で精製して、化合物 I-4 を 704 mg (91 %) 得た。

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 9.96 (s, 1 H), 7.97 (br s, 1 H), 7.92 (d, 2 H,  $J = 8.4$  Hz), 7.85 (d, 2 H,  $J = 8.4$  Hz), 7.67 (d, 2 H,  $J = 1.8$  Hz), 7.66 (t, 1 H,  $J = 1.8$  Hz), 1.38 (s, 18 H).

化合物 I-4 150 mg (0.45 mmol)、2,4-チアゾリジンジオン 52 mg (0.45 mmol) を無水トルエン 10 ml に懸濁し、ピペリジン 11 mg (0.13 mmol) と酢酸 8 mg (0.13 mmol) を無水トルエン 1.4 ml に溶かした溶液を加えて  $120^\circ\text{C}$  にて 3.5 時間還流した。反応液を氷水に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、 $\text{MgSO}_4$  で脱水、溶媒を濃縮して TZ151 を 194 mg (99 %) 得た。

TZ151 : Yellow powder (酢酸エチル/ $n$ -ヘキサン); mp  $> 300^\circ\text{C}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO}-d_6$ ,  $30^\circ\text{C}$ ) 10.43 (s, 1 H), 7.93 (d, 2 H,  $J = 8.4$  Hz), 7.75 (s, 1

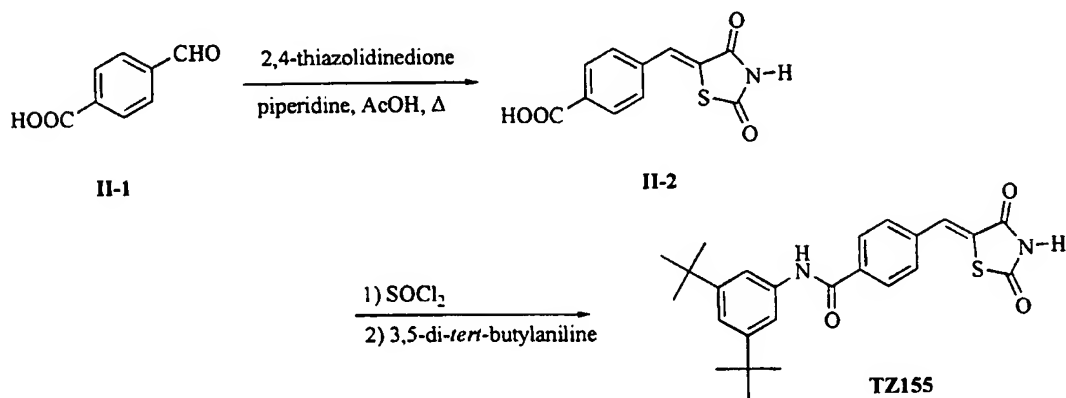
H), 7.74 (d, 2 H,  $J = 1.8$  Hz), 7.63 (m, 3 H), 1.35 (s, 18 H); Anal. Calcd. for  $C_{25}H_{28}N_2O_3S$ , C: 68.78 %, H: 6.46 %, N: 6.42 %; Found C: 68.70%, H: 6.59 %, N: 6.15 %.

### 例 3 : TZ153 の合成

3,5-ジ-tert-ブチル安息香酸(II-1) と m-アミノ安息香酸メチルを出発原料として例 2 の方法に従って TZ153 を合成した。

TZ153 : Pale yellow powder (酢酸エチル/n-ヘキサン); mp 252 °C;  $^1H$ -NMR (400 MHz, DMSO- $d_6$ , 30°C) 10.36 (s, 1 H), 8.16 (br s, 1 H), 7.76 (m, 4 H), 7.63 (t, 1 H,  $J = 1.8$  Hz), 7.52 (t, 1 H,  $J = 8.1$  Hz), 7.37 (d, 1 H,  $J = 8.0$  Hz), 1.35 (s, 18 H); Anal. Calcd. for  $C_{25}H_{28}N_2O_3S$ , C: 68.78 %, H: 6.46 %, N: 6.42 %; Found C: 68.81 %, H: 6.60 %, N: 6.59 %.

### 例 4 : TZ155 の合成



p-ホルミル安息香酸(II-1) 1.00 g (6.67 mmol)、2,4-チアゾリジンジオン 858 mg (7.33 mmol) を無水トルエン 40 ml に懸濁した。ピペリジン 170 mg (2.00 mmol)、酢酸 120 mg (2.00 mmol) を無水トルエン 20 ml に溶かした溶液を加え、120 °Cで6時間還流した。反応液を室温まで冷やし、析出した結晶を濾取し、

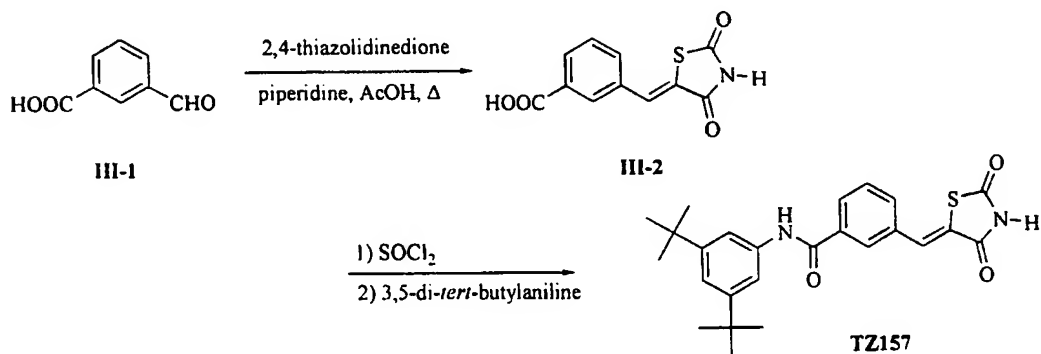
トルエン、ベンゼン、20%アセトン水溶液で洗浄し、乾燥して、化合物 II-2 を 1.57 g (94 %) 得た。

$^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ ,  $30^\circ\text{C}$ ) 8.04 (d, 2 H,  $J = 8.4$  Hz), 7.79 (s, 1 H), 7.70 (d, 2 H,  $J = 8.4$  Hz).

化合物 II-2 250 mg (1.00 mmol) を無水ベンゼン 12 ml に懸濁し、 $\text{SOCl}_2$  627 mg (5.27 mmol) を加えて、14 時間還流した。 $\text{SOCl}_2$  を留去した後、無水ベンゼン 10 ml に懸濁し、3,5-ジ-tert-ブチルアニリン 210 mg (1.00 mmol)、無水ピリジン 4 ml を加え、室温で 2 時間攪拌した。反応液に氷を浮かべた 2 N 塩酸を加え、酢酸エチルで抽出した。有機層を食塩水で洗い、 $\text{MgSO}_4$  で脱水、濃縮後、シリカゲルカラムクロマトグラフィー (酢酸エチル:n-ヘキサン = 3:2) で精製して、TZ155 を 390 mg (89 %) 得た。

TZ155 : Pale yellow powder (酢酸エチル/n-ヘキサン); mp  $266-267^\circ\text{C}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ ,  $30^\circ\text{C}$ ) 10.20 (s, 1 H), 8.08 (d, 2 H,  $J = 8.4$  Hz), 7.87 (s, 1 H), 7.74 (d, 2 H,  $J = 8.4$  Hz), 7.69 (d, 1 H,  $J = 1.5$  Hz), 7.16 (t, 1 H,  $J = 1.5$  Hz), 1.30 (s, 18 H); Anal. Calcd. for  $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_3\text{S}$ , C: 68.78 %, H: 6.46 %, N: 6.42 %, Found C: 68.52 %, H: 6.52 %, N: 6.37 %.

#### 例 5 : TZ157 の合成



m-ホルミル安息香酸(III-1) 800 mg (5.33 mmol)、2,4-チアゾリジンジオン 686

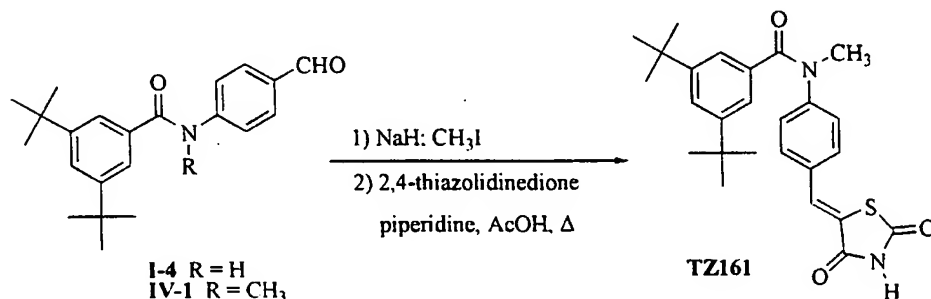
mg (5.87 mmol) を無水トルエン 40 ml に懸濁した。ピペリジン 136 mg (1.60 mmol)、酢酸 96 mg (1.60 mmol) を無水トルエン 16 ml に溶解した溶液を加え、120 °C で 4.5 時間還流した。反応液を室温まで冷やし、析出した結晶を濾取し、トルエン、ベンゼン、20 % アセトン水溶液で洗浄し、乾燥して、化合物 III-2 を 1.017 g (77 %) 得た。

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 8.14 (s, 1 H), 8.01 (d, 1 H, J = 7.7 Hz), 7.86 (s, 1 H), 7.85 (d, 1 H, J = 7.7 Hz), 7.66 (t, 1 H, J = 7.7 Hz).

化合物 III-2 250 mg (1.00 mmol) を無水ベンゼン 14 ml に懸濁し、SOCl<sub>2</sub> 627 mg (5.27 mmol) を加えて、14 時間還流した。SOCl<sub>2</sub> を留去した後、無水ベンゼン 10 ml に懸濁し、3,5-ジ-tert-ブチルアニリン 210 mg (1.00 mmol)、無水ピリジン 4 ml を加え、室温で 2 時間攪拌した。反応液に氷を浮かべた 2 N 塩酸を加え、酢酸エチルで抽出した。有機層を、食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮後、シリカゲルカラムクロマトグラフィー (酢酸エチル : n-ヘキサン = 3 : 4) で精製して、TZ157 を 292 mg (67 %) 得た。

TZ157 : Colorless needles (酢酸エチル / n-ヘキサン); mp 263 °C; <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 10.20 (s, 1 H), 8.15 (s, 1 H), 8.04 (d, 1 H, J = 7.7 Hz), 7.87 (s, 1 H), 7.78 (d, 1 H, J = 7.7 Hz), 7.69 (t, 1 H, J = 7.7 Hz), 7.67 (d, 2 H, J = 1.5 Hz), 7.17 (t, 1 H, J = 1.5 Hz), 1.30 (s, 18H); Anal. Calcd. for C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>S, C: 68.78 %, H: 6.46 %, N: 6.42 %, Found C: 68.82 %, H: 6.65 %, N: 6.56 %.

#### 例 6 : TZ161 の合成



NaH 97.6 mg (60 %、2.45 mmol)をn-ヘキサンで洗い、DMF 1 mlに懸濁した。アルデヒド I-4 (例2参照) 550 mg (1.63 mmol)をDMF 10 mlに溶かして加え、室温で20分攪拌した。ヨウ化メチル 0.19 ml (3.05 mmol)を加え、45分攪拌した。DMFを留去し、水を加えて塩化メチレンで抽出した。有機層を食塩水で洗い、MgSO<sub>4</sub>で脱水、溶媒を濃縮した。残査をシリカゲルカラムクロマトグラフィー(酢酸エチル:n-ヘキサン=1:3)で精製して、化合物 IV-1 を 389 mg (68 %) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 9.90 (s, 1 H), 7.73 (d, 2 H, J = 8.4 Hz), 7.31 (t, 1 H, J = 1.8 Hz), 7.31 (t, 1 H, J = 1.8 Hz), 7.15 (d, 2 H, J = 8.4 Hz), 7.13 (d, 2 H, J = 1.8 Hz), 3.56 (s, 3 H), 1.14 (s, 18 H).

化合物 IV-1 385 mg (1.10 mmol)、2,4-チアゾリジンジオン 128 mg (1.10 mmol)を無水トルエン 8 mlに懸濁し、ピペリジン 26 mg (0.33 mmol)と酢酸 20 mg (0.33 mmol)を無水トルエン 3 mlに溶解した溶液を加えて120 °Cにて1.5時間還流した。反応液を氷水に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、MgSO<sub>4</sub>で脱水、溶媒を濃縮した。残査をシリカゲルカラムクロマトグラフィー(酢酸エチル:n-ヘキサン=1:1)で精製して、TZ161 を 417 mg (84.5 %) 得た。

TZ161 : Yellow plate (酢酸エチル/n-ヘキサン); mp 265 °C; <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 7.70 (s, 1 H), 7.46 (d, 2 H, J = 8.4 Hz), 7.29 (t, 1 H, J = 1.5 Hz), 7.26 (d, 2 H, J = 8.4 Hz), 7.09 (d, 2 H, J = 1.5 Hz), 3.41 (s, 3 H), 1.12 (s, 18 H); Anal. Calcd. for C<sub>26</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>S, C: 69.31 %, H: 6.71 %, N: 6.22 %, Found C: 69.01 %, H: 6.68 %, N: 5.93 %.

#### 例7 : TZ163 の合成

3-(3,5-ジ-tert-ブチルフェニルカルバモイル)ベンズアルデヒド(m-アミノ安息香酸メチルから化合物 I-4と同様に合成)を出発原料として、例6の方法に従ってTZ163を合成した。

TZ163 : Yellow plates (酢酸エチル/n-ヘキサン); mp 195 °C; <sup>1</sup>H-NMR (400 MHz,

DMSO- $d_6$ , 30°C) 7.61 (s, 1 H), 7.46 (t, 1 H,  $J = 7.7$  Hz), 7.38 (m, 2H), 7.27 (t, 1 H,  $J = 1.8$  Hz), 7.14 (br s, 1 H), 7.08 (d, 2 H,  $J = 1.8$  Hz), 3.42 (s, 3 H), 1.11 (s, 18 H); Anal. Calcd. for  $C_{26}H_{30}N_2O_3S$ , C: 69.31 %, H: 6.71 %, N: 6.22 %, Found C: 69.41 %, H: 6.92 %, N: 5.99 %.

#### 例 8 : TZ165 の合成

チアゾリジン II-2 (例 4 参照) および 3,5-ジ-tert-ブチル-N-メチルアニリンを出発原料として、例 4 の方法に従って TZ165 を合成した (79 %)。

TZ165 : Pale yellow prisms (酢酸エチル/n-ヘキサン); mp 253-254 °C;  $^1H$ -NMR (400 MHz, DMSO- $d_6$ , 30°C) 7.67 (s, 1 H), 7.38 (d, 2 H,  $J = 8.4$  Hz), 7.29 (d, 2 H,  $J = 8.4$  Hz), 7.11 (s, 1 H), 6.93 (s, 2 H), 3.42 (s, 3 H), 1.12 (s, 18 H); Anal. Calcd. for  $C_{26}H_{30}N_2O_3S$ , C: 69.31 %, H: 6.71 %, N: 6.22 %, Found C: 69.05 %, H: 6.53 %, N: 6.48 %.

#### 例 9 : TZ167 の合成

チアゾリジン III-2 (例 5 参照) および 3,5-ジ-tert-ブチル-N-メチルアニリンを出発原料として、例 5 の方法に従って TZ167 を合成した (76%)。

TZ167 : Colorless prisms (酢酸エチル/n-ヘキサン); mp 238 °C;  $^1H$ -NMR (400 MHz, DMSO- $d_6$ , 30°C) 7.58 (s, 1 H), 7.48 (m, 2 H), 7.23 (br s, 1 H), 7.10 (s, 1 H), 6.93 (d, 2 H,  $J = 1.5$  Hz), 3.44 (s, 3 H), 1.11 (s, 18 H); Anal. Calcd. for  $C_{26}H_{30}N_2O_3S$ , C: 69.31 %, H: 6.71 %, N: 6.22 %, Found C: 69.13 %, H: 6.78 %, N: 6.34 %.

#### 例 10 : TZ175 の合成

2,4-キシリジンとチアゾリジン II-2 (例 4 参照) を出発原料として、例 4 の方法に従って TZ175 を合成した (88 %)。

TZ175 : Pale pink powder (塩化メチレン/メタノール); mp 269 °C;  $^1H$ -NMR (400

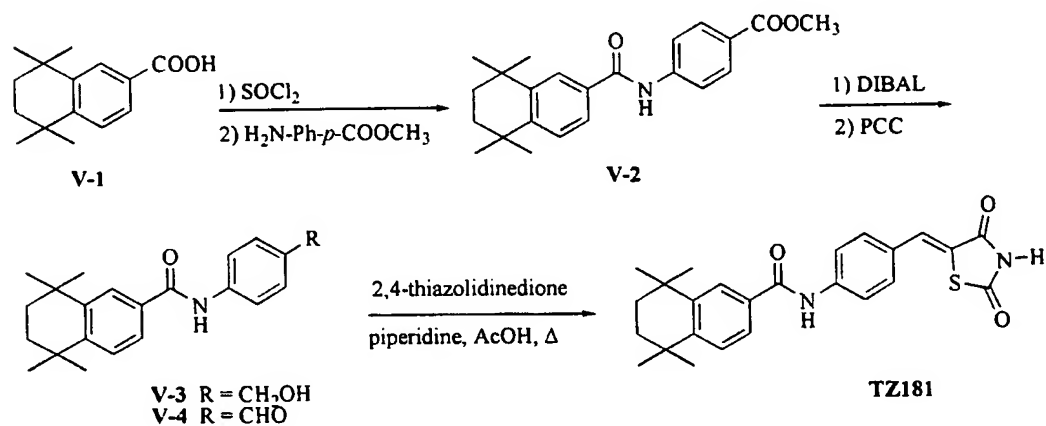
MHz, DMSO- $d_6$ , 30°C) 9.89 (s, 1 H), 8.08 (d, 2 H,  $J = 8.4$  Hz), 7.86 (s, 1 H), 7.73 (d, 2 H,  $J = 8.4$  Hz), 7.21 (d, 1 H,  $J = 8.1$  Hz), 7.08 (s, 1 H), 7.02 (d, 1 H,  $J = 8.1$  Hz), 2.29 (s, 3 H), 2.20 (s, 3 H); Anal. Calcd. for  $C_{19}H_{16}N_2O_3S$ , C: 64.76 %, H: 4.58 %, N: 7.95 %; Found C: 64.51 %, H: 4.67 %, N: 8.07 %.

#### 例 11 : TZ177 の合成

2,4-キシリジンとチアゾリジン III-2 (例 5 参照) を出発原料として、例 5 の方法に従って TZ177 を合成した (31 %)。

TZ177 : Colorless needles (塩化メチレン/メタノール); mp 245 °C;  $^1H$ -NMR (400 MHz, DMSO- $d_6$ , 30°C) 9.90 (s, 1 H), 8.15 (s, 1 H), 8.04 (d, 1 H,  $J = 7.7$  Hz), 7.87 (s, 1 H), 7.79 (d, 1 H,  $J = 8.1$  Hz), 7.68 (t, 1 H,  $J = 7.7$  Hz), 7.23 (d, 1 H,  $J = 8.1$  Hz), 7.09 (s, 1 H), 7.03 (d, 1 H,  $J = 8.1$  Hz), 2.29 (s, 3 H), 2.21 (s, 3 H); Anal. Calcd. for  $C_{19}H_{16}N_2O_3S$ , C: 64.76%, H: 4.58 %, N: 7.95 %; Found C: 64.57 %, H: 4.41 %, N: 7.89 %.

#### 例 12 : TZ181 の合成



5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチル-2- ナフトエ酸 (V-1) 700 mg (3.01 mmol) をチオニルクロライド 8 ml に懸濁し、DMF を 1 滴加えて室温で 2

時間攪拌した。チオニルクロライドを留去し、p-アミノ安息香酸メチル 450 mg (2.98 mmol) および 4-ジメチルアミノピリジン 5 mg を加え、無水ピリジン 20 ml に溶かし、室温で一晩攪拌した。反応液を 2 N 塩酸に開け、酢酸エチルで抽出した。有機層を 2 N 塩酸、水、食塩水で洗い、 $\text{Na}_2\text{SO}_4$  で脱水し、濃縮して、化合物 V-2 を得た (97 %)。

化合物 V-2 183 mg (0.50 mmol) を THF 10 ml に溶かし、 $-45^\circ\text{C}$  にて DIBAL 1.5 ml (1 M トルエン溶液、1.5 mmol) を徐々に加えた。30 分後、反応液を 2 N 塩酸に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、 $\text{Na}_2\text{SO}_4$  で脱水、溶媒を濃縮した。残渣をシリカゲルカラムクロマトグラフィー (酢酸エチル : 塩化メチレン = 1 : 3) で精製して、化合物 V-3 を 142 mg (84 %) 得た。

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 7.86 (d, 1 H,  $J = 2.2$  Hz), 7.78 (br s, 1 H), 7.63 (d, 2 H,  $J = 8.4$  Hz), 7.55 (dd, 1 H,  $J = 2.0, 8.2$  Hz), 7.40 (d, 1 H,  $J = 8.8$  Hz), 7.37 (d, 2 H,  $J = 8.4$  Hz), 4.68 (s, 2 H), 1.72 (s, 4 H), 1.33 (s, 6 H), 1.31 (s, 6 H)。

化合物 V-3 140 mg (0.42 mmol) をメタノールフリー塩化メチレン 10 ml に溶かし、PCC 100 mg (0.46 mmol) を加え、室温で 1 時間攪拌した。反応液を濃縮し、シリカゲルカラムクロマトグラフィー (塩化メチレン) で精製して、化合物 V-4 を 99 mg (71 %) 得た。

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 9.95 (s, 1 H), 7.92 (br s, 1 H), 7.91 (d, 2 H,  $J = 8.8$  Hz), 7.87 (d, 1 H,  $J = 1.8$  Hz), 7.84 (d, 2 H,  $J = 8.8$  Hz), 7.56 (dd, 1 H,  $J = 2.0, 8.3$  Hz), 7.43 (d, 1 H,  $J = 8.4$  Hz), 1.73 (s, 4 H), 1.34 (s, 6 H), 1.32 (s, 6 H)。

化合物 V-4 73 mg (0.22 mmol)、2,4-チアゾリジンジオン 30 mg (0.26 mmol) を無水トルエン 4 ml に懸濁した。ピペリジン 173  $\mu\text{l}$  と酢酸 100  $\mu\text{l}$  を無水トルエン 25 ml に溶かし、その溶液 3 ml を加えて  $120^\circ\text{C}$  にて 2 時間還流した。反応液を氷水に注ぎ込み、酢酸エチルで抽出した。有機層を 2 N 塩酸、水で洗い、 $\text{Na}_2\text{SO}_4$  で脱水、溶媒を濃縮して TZ181 を 100 mg (定量的) 得た。

TZ181 : Yellow needles (酢酸エチル/n-ヘキサン); mp 288-290 °C; <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 12.52 (s, 1 H), 10.36 (s, 1 H), 7.94 (d, 2 H, J = 8.8 Hz), 7.88 (d, 1 H, J = 2.2 Hz), 7.76 (s, 1 H), 7.71 (dd, 2 H, J = 2.2, 8.4 Hz), 7.60 (d, 2 H, J = 8.8 Hz), 7.48 (d, 1 H, J = 98.3 Hz), 1.68 (s, 4 H), 1.31 (s, 6 H), 1.28 (s, 6 H); Anal. Calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>S, C: 69.10 %, H: 6.03 %, N: 6.45 %; Found C: 69.05 %, H: 6.23 %, N: 6.55 %.

#### 例 13 : TZ183 の合成

5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチル-2- ナフトエ酸(V-1) と m-アミノ安息香酸メチルを出発原料として、例 12 の方法に従って TZ183 を合成した。  
TZ183 : Colorless powder (酢酸エチル/n-ヘキサン); mp 183 °C; <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 10.29 (s, 1 H), 8.15 (s, 1 H), 7.88 (d, 1 H, J = 1.8 Hz), 7.76 (d, 1 H, J = 1.8 Hz), 7.26 (s, 1 H), 7.26 (s, 1 H), 6.71 (dd, 1 H, J = 8.4 Hz, 1.8 Hz), 6.50 (t, 1 H, J = 7.7 Hz), 6.49 (d, 1 H, J = 8.1 Hz), 6.35 (d, 1 H, J = 2.1 Hz), 1.69 (s, 4 H), 1.31 (s, 6 H), 1.28 (s, 6 H); Anal. Calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>S, C: 69.10 %, H: 6.03 %, N: 6.45 %; Found C: 68.81 %, H: 5.92 %, N: 6.51 %.

#### 例 14 : TZ185 の合成

5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチル-2- ナフチルアミンとチアゾリジン II-2 (例 4 参照) を出発原料として、例 4 の方法に従って TZ185 を合成した。

TZ185 : Pale orange plates (酢酸エチル/n-ヘキサン); mp 234 °C; <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30 °C) 10.18 (s, 1 H), 8.07 (d, 2 H, J = 8.4 Hz), 7.86 (s, 1 H), 7.73 (d, 2 H, J = 8.4 Hz), 7.68 (d, 1 H, J = 2.2 Hz), 7.57 (dd, 1 H, J = 8.4 Hz, 2.2 Hz), 7.28 (d, 1 H, J = 8.4 Hz), 1.65 (s, 4 H), 1.25 (s, 6 H), 1.24 (s, 6 H); Anal. Calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>S, C: 69.10 %, H: 6.03 %, N: 6.45 %;

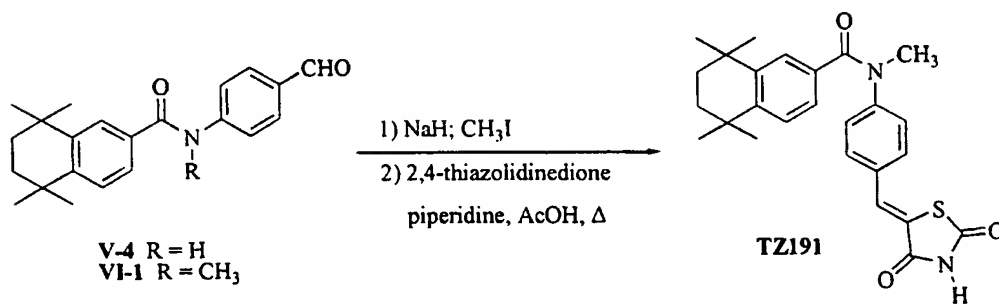
Found C: 69.40 %, H: 6.10 %, N: 6.55 %.

### 例 15 : TZ187 の合成

5,6,7,8-テトラヒドロ-5,5,8,8- テトラメチル-2- ナフチルアミンとチアゾリジン III-2 (例 5 参照) を出発原料として、例 5 の方法に従って TZ187 を合成した。

TZ187 : Colorless plates (酢酸エチル/n-ヘキサン); mp 187 °C; <sup>1</sup>H-NMR (40 MHz, DMSO-d<sub>6</sub>, 30°C) 10.18 (s, 1 H), 8.14 (s, 1 H), 8.03 (d, 2 H, J = 7.7 Hz), 7.87 (s, 1 H), 7.78 (d, 1 H, J = 7.7 Hz), 7.68 (t, 1 H, J = 7.7 Hz), 7.68 (d, 1 H, J = 2.2 Hz), 7.56 (dd, 1 H, J = 8.8 Hz, 2.2 Hz), 7.29 (d, 1 H, J = 8.4 Hz), 1.65 (s, 4 H), 1.26 (s, 6 H), 1.24 (s, 6 H); Anal. Calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>S, C: 69.10 %, H: 6.03 %, N: 6.45 %; Found C: 68.81%, H: 6.21 %, N: 6.37 %.

### 例 16 : TZ191 の合成



NaH 18 mg (60 %、0.45 mmol) を n-ヘキサンで洗い、DMF 1 ml に懸濁した。アルデヒド V-4 (例 12 参照) 100 mg (0.30 mmol) を DMF 4 ml に溶かして加え、室温で 15 分攪拌した。ヨウ化メチル 0.07 ml (1.12 mmol) を加え、30 分攪拌した。DMF を留去し、水を加えて塩化メチレンで抽出した。有機層を食塩水で洗い、MgSO<sub>4</sub> で脱水後、溶媒を濃縮した。残渣をシリカゲルカラムクロマトグラフィー (酢酸エチル : n-ヘキサン = 1 : 2) で精製して、化合物 VI-1 を 388.9 mg (63 %)

得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 9.92 (s, 1 H), 7.75 (d, 2 H, J = 8.4 Hz), 7.24 (dd, 1 H, J = 8.1, 1.8 Hz), 7.19 (d, 1 H, J = 8.4 Hz), 7.18 (d, 1 H, J = 8.4 Hz), 7.04 (d, 1 H, J = 1.8 Hz), 3.55 (s, 3 H), 1.60 (m, 4 H), 1.20 (s, 6 H), 0.93 (s, 6 H).

化合物 VI-1 60 mg (0.17 mmol)、2,4-チアゾリジンジオン 20 mg (0.17 mmol) を無水トルエン 4 ml に懸濁し、ピペリジン 4.4 mg (0.052 mmol) と酢酸 3.1 mg (0.052 mmol) を無水トルエン 0.5 ml に溶解した溶液を加えて 120 °C にて 40 分 還流した。反応液を氷水に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で 洗い、MgSO<sub>4</sub> で脱水、溶媒を濃縮した。残渣をシリカゲルカラムクロマトグラフ ー (酢酸エチル : n-ヘキサン = 1 : 3) で精製して、TZ191 を 417 mg (93 %) 得 た。

TZ191 : Yellow powder (酢酸エチル / n-ヘキサン); mp 235 °C; <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 7.71 (s, 1 H), 7.48 (d, 2 H, J = 8.8 Hz), 7.28 (d, 2H, J = 8.4 Hz), 7.27 (d, 1 H, J = 8.4 Hz), 7.22 (dd, 1 H, J = 8.4, 1.5 Hz), 6.98 (d, 1 H, J = 1.8 Hz), 3.40 (s, 3 H), 1.53 (m, 4 H), 1.17 (s, 6H), 0.89 (s, 6 H); Anal. Calcd. for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>S, C: 69.62 %, H: 6.29 %, N: 6.24 %, Found C: 69.33 %, H: 6.38 %, N: 6.31 %.

#### 例 17 : TZ193 の合成

3-(5,6,7,8- テトラヒドロ-5,5,8,8- テトラメチル-2- ナフチルカルバモイル) ベンズアルデヒド (m-アミノ安息香酸メチルから化合物 V-4 と同様に合成) を 出発原料として、例 16 の方法に従って TZ193 を合成した。

TZ193 : Colorless plates (酢酸エチル / n-ヘキサン); mp 188 °C; <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 7.64 (s, 1 H), 7.47 (t, 1 H, J = 7.7 Hz), 7.38 (m, 2 H), 7.24 (d, 1 H, J = 8.1 Hz), 7.16 (dd, 1 H, J = 8.4, 1.8 Hz), 7.03 (d, 1 H, J = 1.8 Hz), 3.41 (s, 3 H), 1.52 (s, 4 H), 1.14 (s, 6 H), 0.91 (s, 6 H); Anal.

Calcd. for  $C_{26}H_{28}N_2O_3S$ , C: 69.62 %, H: 6.29 %, N: 6.24 %, Found C: 69.65 %, H: 6.16 %, N: 6.08 %.

例 18 : TZ195 の合成

チアゾリジン II-2 (例 4 参照) および 5,6,7,8-テトラヒドロ-N,5,5,8,8-ペ  
ンタメチル-2- ナフチルアミンとから例 4 の方法に従って合成した (80 %)。

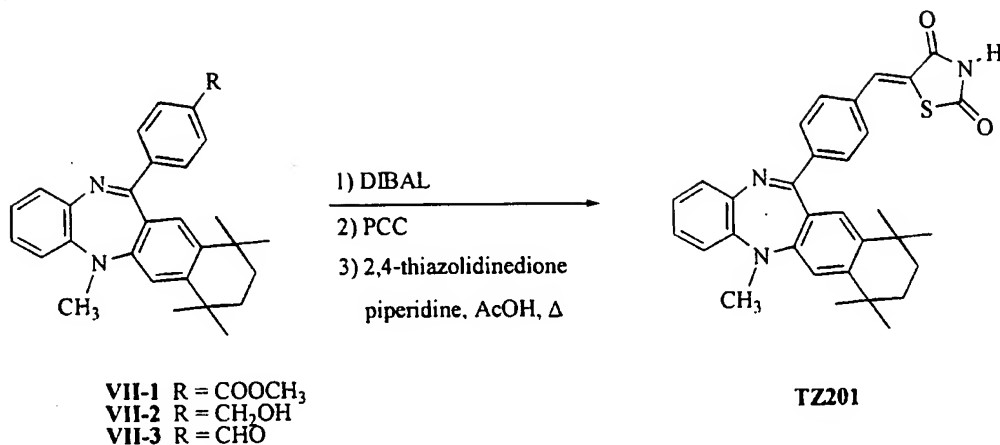
TZ195 : Pale yellow plates (酢酸エチル/n-ヘキサン); mp 233 °C;  $^1H$ -NMR (400 MHz, DMSO- $d_6$ , 30°C) 7.69 (s, 1 H), 7.39 (d, 2 H, J = 8.1 Hz), 7.31 (d, 2 H, J = 8.1 Hz), 7.26 (d, 2 H, J = 8.8 Hz), 7.06 (dd, 1 H, J = 8.4, 2.6 Hz), 6.83 (br s, 1 H), 3.37 (s, 3 H), 1.50 (m, 4 H), 1.16 (s, 6 H), 0.91 (s, 6 H); Anal. Calcd. for  $C_{26}H_{28}N_2O_3S$ , C: 69.62 %, H: 6.29 %, N: 6.24 %, Found C: 69.38 %, H: 6.42 %, N: 6.02 %.

例 19 : TZ197 の合成

チアゾリジン III-2 (例 5 参照) および 5,6,7,8-テトラヒドロ-N,5,5,8,8-ペ  
ンタメチル-2- ナフチルアミンから例 5 の方法に従って合成した (70 %)。

TZ197 : Pale yellow prisms (酢酸エチル/n-ヘキサン); mp 237 °C;  $^1H$ -NMR (400 MHz, DMSO- $d_6$ , 30°C) 7.59 (s, 1 H), 7.48 (d, 1 H, J = 7.0 Hz), 7.42 (m, 2 H), 7.24 (d, 1 H, J = 8.4 Hz), 7.19 (s, 1 H), 7.04 (dd, 1 H, J = 8.4, 2.2 Hz), 6.85 (d, 1 H, J = 2.2 Hz), 3.41 (s, 3 H), 1.51 (s, 4 H), 1.14 (s, 6 H), 0.91 (s, 6 H); Anal. Calcd. for  $C_{26}H_{28}N_2O_3S$ , C: 69.62 %, H: 6.29 %, N: 6.24 %, Found C: 69.51 %, H: 6.37 %, N: 6.27 %.

## 例 20 : TZ201 の合成



エステル体 VII-1 110 mg (0.24 mmol) を THF 10 ml に溶かし、 $-20^{\circ}\text{C}$  にて DIBAL 1.5 ml (1 M トルエン溶液、1.5 mmol) を徐々に加えた。3 時間後、反応液を 2 N 塩酸に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、 $\text{Na}_2\text{SO}_4$  で脱水、溶媒を濃縮した。残査をシリカゲルカラムクロマトグラフィー (酢酸エチル : 塩化メチレン = 1 : 4) で精製して化合物 VII-2 を 100 mg (97 %) 得た。

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 7.81 (d, 2 H,  $J = 8.4$  Hz), 7.40 (d, 2 H,  $J = 8.4$  Hz), 7.31 (d, 1 H,  $J = 7.3$  Hz), 7.13 (dt, 1 H,  $J = 1.8, 7.3$  Hz), 7.08 (dt, 1 H,  $J = 1.5, 7.3$  Hz), 6.97 (dd, 1 H,  $J = 1.5, 7.7$  Hz), 6.94 (s, 1 H), 6.92 (s, 1 H), 4.77 (d, 2 H,  $J = 4.4$  Hz), 3.25 (s, 3 H), 1.64 (m, 4 H), 1.32 (s, 3 H), 1.26 (s, 3 H), 1.14 (s, 3 H), 1.05 (s, 3 H)。

化合物 VII-2 100 mg (0.24 mmol) をメタノールフリー塩化メチレン 10 ml に溶かし、PCC 60 mg (0.28 mmol) を加え、室温で 1 時間攪拌した。反応液を濃縮し、シリカゲルカラムクロマトグラフィー (酢酸エチル : 塩化メチレン = 1 : 50) で精製して、化合物 VII-3 を 72 mg (72 %) 得た。

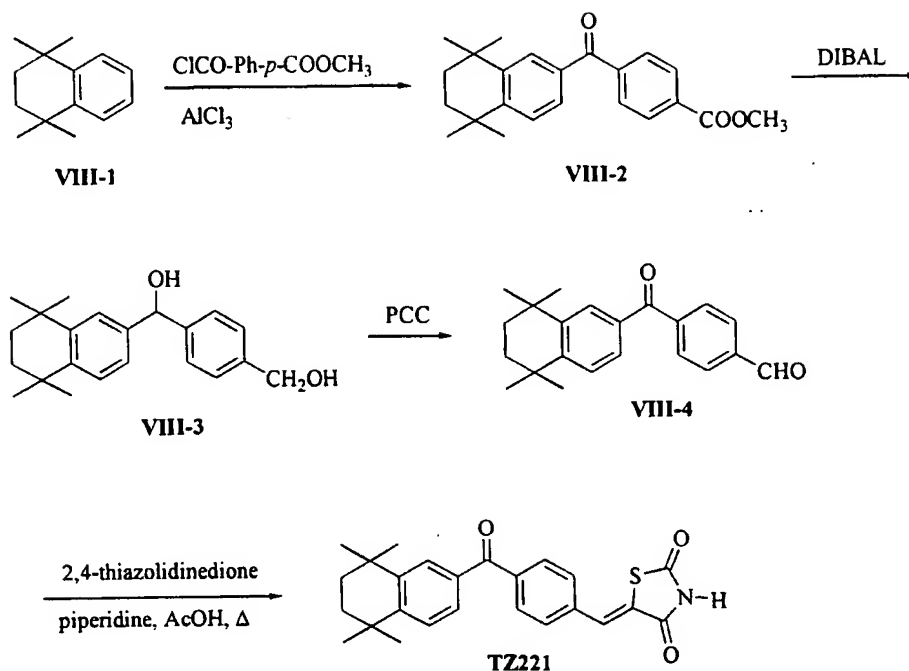
$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 10.10 (s, 1 H), 7.98 (d, 2 H,  $J = 8.0$  Hz), 7.92 (d, 2 H,  $J = 8.8$  Hz), 7.32 (d, 1 H,  $J = 7.7$  Hz), 7.17 (dt, 1 H,  $J = 1.5, 8.0$  Hz), 7.10 (dt, 1 H,  $J = 1.5, 7.7$  Hz), 6.98 (dd, 1 H,  $J = 1.5, 8.1$  Hz), 6.93 (s,

1 H), 6.86 (s, 1 H), 3.26 (s, 3 H), 1.65 (m, 4 H), 1.32 (s, 3 H), 1.27 (s, 3 H), 1.12 (s, 3 H), 1.04 (s, 3 H).

化合物 VII-3 70 mg (0.17 mmol)、2,4-チアゾリジンジオン 20 mg (0.17 mmol) を無水トルエン 4 ml に懸濁した。ピペリジン 173  $\mu$ l と酢酸 100  $\mu$ l を無水トルエン 25 ml に溶かし、その溶液 2.5 ml を加えて 120 °C にて 2 時間還流した。反応液を氷水に注ぎ込み、酢酸エチルで抽出した。有機層を 2 N 塩酸、水で洗い、 $\text{Na}_2\text{SO}_4$  で脱水、溶媒を濃縮して TZ201 を 73 mg (84 %) 得た。

TZ201 : Red needles (酢酸エチル/メタノール); mp > 300 °C;  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ , 30°C) 12.62 (s, 1 H), 7.83 (s, 1 H), 7.82 (d, 2 H,  $J = 8.7\text{Hz}$ ), 7.69 (d, 2 H,  $J = 8.3\text{Hz}$ ), 7.16-7.22 (m, 2 H), 7.09 (m, 2 H), 7.06 (s, 1 H), 6.90 (s, 1 H), 3.21 (s, 3 H), 1.62 (m, 4 H), 1.30 (s, 3 H), 1.26 (s, 3 H), 1.13 (s, 3 H), 1.03 (s, 3 H); Anal. Calcd. for  $\text{C}_{32}\text{H}_{31}\text{N}_3\text{O}_2\text{S} \cdot \text{H}_2\text{O}$ , C: 71.23 %, H: 6.16 %, N: 7.79 %; Found C: 71.12 %, H: 6.02 %, N: 7.71 %.

## 例 21 : TZ221 の合成



1, 2, 3, 4-テトラヒドロ-1, 1, 4, 4- テトラメチルナフタレン (VIII-1) 1.00 g (5.32 mmol)およびテレフタル酸モノメチルエステルクロリド 1.06 g (5.32 mmol)をメタノールフリー塩化メチレン 20ml に溶かし、塩化アルミニウム 1.42 g (10.64 mmol)を氷冷下に加え、その後 30 分還流した。反応液を氷水にあげ、酢酸エチルで抽出した。有機層を水、食塩水で洗い、 $\text{MgSO}_4$  で脱水、濃縮後、シリカゲルカラムクロマトグラフィー (酢酸エチル:ヘキサン= 1:20 ついで 1:10) で精製して、化合物 VIII-2 を 1.30 g (70%) 得た。 $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 8.14 (d, 2 H,  $J = 8.4$  Hz), 7.83 (d, 2 H,  $J = 8.4$  Hz), 7.78 (d, 1 H,  $J = 1.8$  Hz), 7.53 (dd, 1 H,  $J = 8.4, 1.8$  Hz), 7.40 (d, 1 H,  $J = 8.0$  Hz), 3.97 (s, 3 H), 1.72 (s, 4 H), 1.32 (s, 6 H), 1.29 (s, 6 H)。

化合物 VIII-2 1.20 g (3.43 mmol)をアルゴン置換下、THF 15 ml にとかして、 $-78^\circ\text{C}$ にて攪拌しながら DIBAL 13.7ml (1 M トルエン溶液、13.7 mmol)を徐々に滴下した。1 時間後、反応液を 1 N 塩酸に注ぎ込み、酢酸エチルで抽出した。

有機層を食塩水で洗い、 $\text{MgSO}_4$  で脱水、濃縮後、シリカゲルカラムクロマトグラフィー（酢酸エチル：ヘキサン＝ 1 : 3）で精製したところ、ケトンのみが還元された化合物（937.5 mg）を得たので、再び、DIBAL により 0 °C、30 分にて還元し、同様の後処理により化合物 VIII-3 を 896 mg (81 %) 得た。

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 7.40 (d, 2 H,  $J = 8.1$  Hz), 7.34 (m, 3 H), 7.25 (d, 1 H,  $J = 8.0$  Hz), 7.05 (dd, 1 H,  $J = 8.0, 1.8$  Hz), 5.80 (s, 1 H), 4.68 (s, 2 H), 2.15 (br s, 1 H), 1.67 (s, 4 H), 1.26 (s, 6 H), 1.25 (s, 6 H).

アルミナ 4.70 g と PCC 2.65 g (12.3 mmol) をメタノールフリー塩化メチレン 10 ml にアルゴン置換下懸濁し、化合物 VIII-3 810 mg (2.50 mmol) をメタノールフリー塩化メチレン 10 ml に溶解して徐々に加えた。1 時間後、反応液を濃縮し、シリカゲルカラムクロマトグラフィー（酢酸エチル：*n*-ヘキサン＝ 1 : 7）により精製して、化合物 VIII-4 を 798 mg (99.7%) 得た。

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 10.14 (s, 1 H), 8.00 (d, 2 H,  $J = 8.4$  Hz), 7.91 (d, 2 H,  $J = 8.1$  Hz), 7.80 (d, 1 H,  $J = 1.8$  Hz), 7.53 (dd, 1 H,  $J = 8.4, 2.2$  Hz), 7.41 (d, 1 H,  $J = 8.1$  Hz), 1.73 (s, 4 H), 1.32 (s, 6 H), 1.30 (s, 6 H).

化合物 VIII-4 790 mg (2.47 mmol)、2,4-チアゾリジンジオン 319 mg (2.72 mmol) を無水トルエン 20 ml に懸濁し、ピペリジン 63 mg (0.74 mmol) と酢酸 45 mg (0.74 mmol) を無水トルエン 8 ml に溶解した溶液を加えて 120 °C にて 3 時間還流した。反応液を氷水に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、 $\text{MgSO}_4$  で脱水、濃縮した後、シリカゲルカラムクロマトグラフィー（酢酸エチル：ヘキサン＝ 1 : 2）で精製して、TZ221 を 328 mg (32 %) 得た。

TZ221 : Colorless powder (酢酸エチル/*n*-ヘキサン); mp 204 °C;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 8.46 (s, 1 H), 7.90 (d, 2 H,  $J = 8.4$  Hz), 7.80 (d, 1 H,  $J = 1.8$  Hz), 7.60 (d, 2 H,  $J = 8.1$  Hz), 7.53 (dd, 1 H,  $J = 8.0, 1.8$  Hz), 7.41 (d, 1 H,  $J = 8.1$  Hz), 1.73 (s, 4 H), 1.33 (s, 6 H), 1.31 (s, 6 H); Anal. Calcd. for  $\text{C}_{25}\text{H}_{25}\text{NO}_3\text{S}$ , C, 71.57; H, 6.01%; N, 3.34%; Found, C, 71.28%; H, 5.92%; N, 3.09%.

## 例 22 : TZ223 の合成

1, 2, 3, 4-テトラヒドロ-1, 1, 4, 4- テトラメチルナフタレン (VIII-1) とイソフタル酸モノメチルエステルクロリドを出発原料として、例 21 の方法に従って TZ223 を合成した。

TZ223 : Yellow prisms (酢酸エチル/n-ヘキサン); mp 189 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 8.46 (br s, 1 H), 7.91 (s, 1 H), 7.90 (s, 1 H), 7.86 (d, 1 H, J = 7.7 Hz), 7.81 (d, 1 H, J = 1.8 Hz), 7.70 (d, 1 H, J = 7.7 Hz), 7.61 (t, 1 H, J = 7.7 Hz), 7.52 (dd, 1 H, J = 8.1, 1.8 Hz), 7.42 (d, 1 H, J = 8.1 Hz), 1.73 (s, 4 H), 1.33 (s, 6 H), 1.31 (s, 6 H); Anal. Calcd. for C<sub>23</sub>H<sub>23</sub>NO<sub>3</sub>S, C: 71.57 %, H: 6.01 %, N: 3.34 %; Found, C: 71.64 %, H: 6.16 %, N: 3.19 %.

## 例 23 : TZ225 の合成

1, 2, 3, 4-テトラヒドロ-1, 1, 4, 4, 6- ペンタメチルナフタレンとテレフタル酸モノメチルエステルクロリドを出発原料として、例 21 の方法に従って TZ225 を合成した。

TZ225 : Yellow prisms (酢酸エチル/n-ヘキサン); mp 245 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 8.67 (s, 1 H), 7.91 (d, 1 H, J = 8.4 Hz), 7.90 (s, 1 H), 7.58 (d, 1 H, J = 8.8 Hz), 7.26 (s, 1 H), 7.21 (s, 1 H), 2.33 (s, 3 H), 1.70 (s, 4 H), 1.32 (s, 6 H), 1.22 (s, 6 H); Anal. Calcd. for C<sub>26</sub>H<sub>27</sub>NO<sub>3</sub>S, C: 72.03 %, H: 6.28 %, N: 3.23 %; Found, C: 71.87 %, H: 6.35 %, N: 3.14 %.

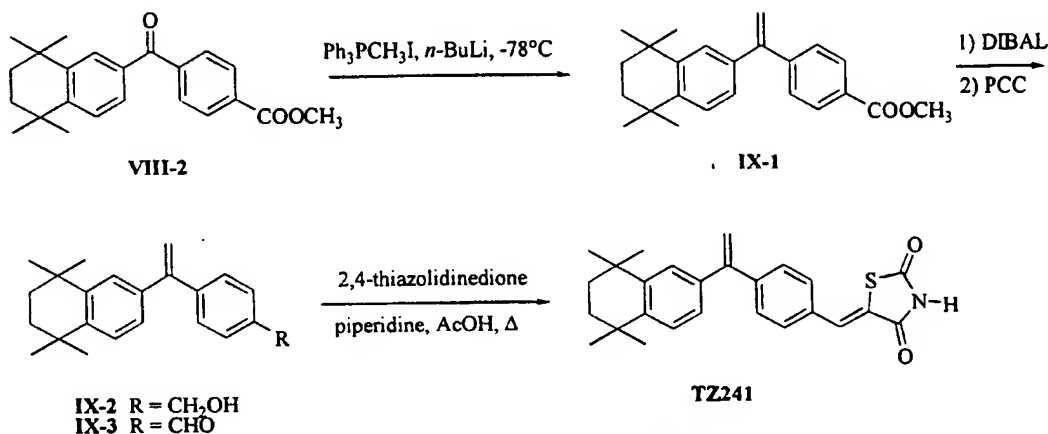
## 例 24 : TZ227 の合成

1, 2, 3, 4-テトラヒドロ-1, 1, 4, 4, 6- ペンタメチルナフタレンとイソフタル酸モノメチルエステルクロリドを出発原料として、例 21 の方法に従って TZ227 を合成した。

TZ227 : Pale yellow prisms (酢酸エチル/n-ヘキサン); mp 191 °C; <sup>1</sup>H-NMR (400

MHz,  $\text{CDCl}_3$ ) 8.40 (s, 1 H), 7.87–7.92 (m, 2 H), 7.86 (s, 1 H), 7.69 (d, 1 H,  $J = 7.7$  Hz), 7.59 (t, 1 H,  $J = 7.7$  Hz), 7.25 (s, 1 H), 7.23 (s, 1 H), 2.32 (s, 3 H), 1.71 (s, 4 H), 1.33 (s, 6 H), 1.22 (s, 6 H); Anal. Calcd. for  $\text{C}_{26}\text{H}_{27}\text{NO}_3\text{S}$ , C: 72.03 %, H: 6.28 %, N: 3.23 %; Found, C: 72.21 %, H: 6.37 %, N: 2.96 %.

例 25 : TZ241 の合成



$\text{Ph}_3\text{PCH}_2\text{I}$  4.04 g (10.1 mmol)を 5 ml の THF に懸濁し、 $-78^\circ\text{C}$ で  $n$ -ブチルリチウム 8.36 ml (13.4 mmol)を加え 15 分攪拌した。化合物 VIII-2 2.35 g (6.71 mmol)を 12 ml の THF に溶かして加え 1 時間攪拌した。反応液に水を加え、塩化メチレンで抽出した。有機層を  $\text{MgSO}_4$  で脱水、濃縮し、シリカゲルカラムクロマトグラフィー (酢酸エチル: $n$ -ヘキサン = 1:12.5) で精製して、化合物 IX-1 を 680 mg (30 %)得た。

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 8.00 (d, 2 H,  $J = 8.6$  Hz), 7.43 (d, 2 H,  $J = 8.4$  Hz), 7.26 (d, 1 H,  $J = 8.1$  Hz), 7.22 (d, 1 H,  $J = 1.8$  Hz), 7.07 (dd, 1 H,  $J = 8.3$ , 2.2 Hz), 5.53 (d, 1 H,  $J = 1.1$  Hz), 5.47 (d, 1 H,  $J = 1.1$  Hz), 3.93 (s, 3 H), 1.69 (s, 4 H), 1.30 (s, 6 H), 1.23 (s, 6 H).

化合物 IX-1 675 mg (2.01 mmol)を THF 5 ml に溶かし、 $-78^\circ\text{C}$ にて DIBAL 6.0 ml (1 M トルエン溶液、6.0 mmol)を徐々に加え、その後  $0^\circ\text{C}$ で 30 分攪拌した。反応液を 1 N 塩酸に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、

MgSO<sub>4</sub> で脱水、濃縮した後、シリカゲルカラムクロマトグラフィー（酢酸エチル：n-ヘキサン＝ 1:3）で精製して、化合物 IX-2 を 619mg（定量的）得た。<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 7.35 (m, 4 H), 7.27 (d, 1 H, J = 1.8 Hz), 7.25 (d, 1 H, J = 8.4 Hz), 7.08 (dd, 1 H, J = 8.4, 2.2 Hz), 5.44 (d, 1 H, J = 1.5 Hz), 5.40 (d, 1 H, J = 1.1 Hz), 4.72 (s, 2 H), 1.69 (s, 4 H), 1.29 (s, 6 H), 1.24 (s, 6 H).

化合物 IX-2 620 mg (2.01 mmol) をメタノールフリー塩化メチレン 10 ml に溶かし、PCC 866 mg (4.02 mmol) を加え、室温で 1.5 時間攪拌した。反応液を濃縮し、シリカゲルカラムクロマトグラフィー（酢酸エチル：n-ヘキサン＝ 1:8）で精製して、化合物 IX-3 を 428.5 mg (70%) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 10.03 (s, 1 H), 7.85 (d, 2 H, J = 8.4 Hz), 7.53 (d, 2 H, J = 8.4 Hz), 7.27 (d, 1 H, J = 8.1 Hz), 7.23 (d, 1 H, J = 1.8 Hz), 7.06 (dd, 1 H, J = 8.1, 1.8 Hz), 5.57 (d, 1 H, J = 1.1 Hz), 5.51 (d, 1 H, J = 0.7 Hz), 1.70 (s, 4 H), 1.30 (s, 6 H), 1.24 (s, 6 H).

化合物 XII-4 420 mg (1.37 mmol)、2,4-チアゾリジンジオン 162 mg (1.38 mmol) を取って無水トルエン 8 ml に懸濁し、ピペリジン 32 mg (0.38 mmol) と酢酸 23 mg (0.38 mmol) を無水トルエン 4 ml に溶解した溶液を加えて 120°C にて 2 時間還流した。反応液を氷水に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮した後、シリカゲルカラムクロマトグラフィー（酢酸エチル：n-ヘキサン＝ 1:4）で精製して、TZ241 を 449.2 mg (81 %) 得た。

TZ241 : Pale yellow needles (酢酸エチル/n-ヘキサン); mp 198 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 8.42 (s, 1 H), 7.88 (s, 1 H), 7.48 (m, 4 H), 7.27 (d, 1 H, J = 8.4 Hz), 7.24 (d, 1 H, J = 1.8 Hz), 7.06 (dd, 1 H, J = 8.4, 1.8 Hz), 5.52 (s, 1 H), 5.51 (s, 1 H), 1.70 (s, 4 H), 1.30 (s, 6 H), 1.25 (s, 6 H); Anal. Calcd. for C<sub>26</sub>H<sub>27</sub>NO<sub>2</sub>S, C: 74.79 %, H: 6.52 %, N: 3.35 %; Found C: 74.59 %, H: 6.51 %, N: 3.32 %.

## 例 26 : TZ243 の合成

m-(5,6,7,8- テトラヒドロ-5,5,8,8- テトラメチル-2- ナフトイル) 安息香酸メチルを出発原料として例 25 の方法に従って TZ243 を合成した。

TZ243 : Colorless powder (酢酸エチル/n-ヘキサン); mp 168 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 8.30 (br s, 1 H), 7.85 (s, 1 H), 7.46 (m, 4 H), 7.28 (d, 1 H, J = 8.1 Hz), 7.25 (d, 1 H, J = 2.2 Hz), 7.05 (dd, 1 H, J = 8.1 Hz, 2.2 Hz), 5.51 (d, 1 H, J = 0.7 Hz), 5.46 (d, 1 H, J = 1.1 Hz), 1.70 (s, 4 H), 1.33 (s, 6 H), 1.25 (s, 6 H); Anal. Calcd. for C<sub>26</sub>H<sub>27</sub>NO<sub>2</sub>S · 1/4H<sub>2</sub>O, C: 74.00 %, H: 6.57 %, N: 3.32 %; Found C: 74.00 %, H: 6.60 %, N: 3.36%.

## 例 27 : TZ245 の合成

Ph<sub>3</sub>PCH<sub>3</sub>I 1.09 g (2.70 mmol)を 5 ml の THF に懸濁し、-78 °Cで n-ブチルリチウム 2.22 ml (3.56 mmol)を加え 15 分攪拌した。TZ225 (例 23 参照)800 mg(1.78 mmol)を 6 ml の THF に溶かして加え、1 時間攪拌した。反応液に水を加え、塩化メチレンで抽出した。有機層を MgSO<sub>4</sub> で脱水、濃縮し、シリカゲルカラムクロマトグラフィー (酢酸エチル : n-ヘキサン = 1 : 3) で精製して、TZ245 を 52 mg (6.5 %)得た。

TZ245 : Pale yellow powder (酢酸エチル/n-ヘキサン); mp 281 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 8.29 (s, 1 H), 7.84 (s, 1 H), 7.42 (m, 4 H), 7.12 (s, 1 H), 7.09 (s, 1 H), 5.83 (d, 1 H, J = 1.1 Hz), 5.32 (d, 1 H, J = 1.1 Hz), 1.96 (s, 3 H), 1.70 (s, 4 H), 1.31 (s, 6 H), 1.28 (s, 6 H); Anal. Calcd. for C<sub>27</sub>H<sub>29</sub>NO<sub>2</sub>S, C: 75.14 %, H: 6.77 %, N: 3.25 %; Found C: 74.86 %, H: 6.81 %, N: 3.33 %.

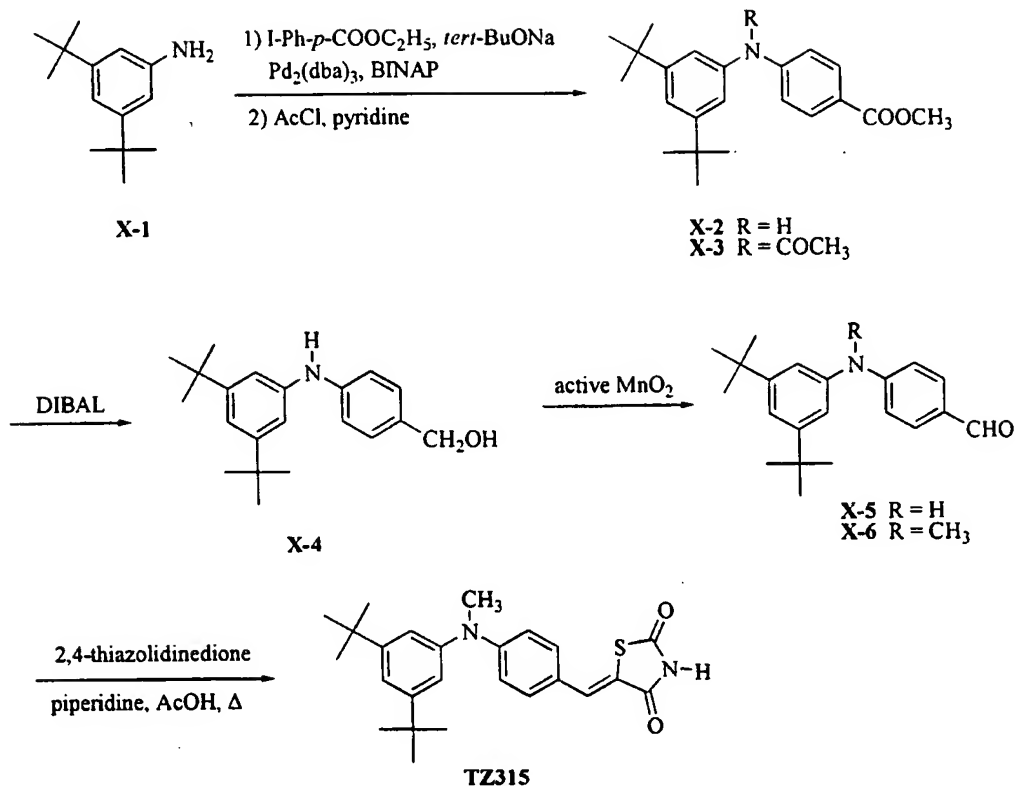
## 例 28 : TZ247 の合成

m-(5,6,7,8- テトラヒドロ-3,5,5,8,8- ペンタメチル-2- ナフトイル) 安息香酸メチルを出発原料として例 25 の方法に従って TZ247 を合成した。

TZ247 : Pale yellow powder (酢酸エチル/n-ヘキサン); mp 185 °C; <sup>1</sup>H-NMR (400

MHz, CDCl<sub>3</sub>) 8.19 (br s, 1 H), 7.79 (s, 1 H), 7.49 (d, 1 H, J = 7.7 Hz), 7.43 (t, 1 H, J = 7.7 Hz), 7.37 (d, 1 H, J = 7.7 Hz), 7.25 (s, 1 H), 7.13 (s, 1 H), 7.12 (s, 1 H), 5.80 (d, 1 H, J = 1.1 Hz), 5.31 (d, 1 H, J = 1.1 Hz), 1.96 (s, 3 H), 1.72 (s, 4 H), 1.32 (s, 6 H), 1.29 (s, 6 H); Anal. Calcd. for C<sub>27</sub>H<sub>29</sub>NO<sub>2</sub>S, C: 75.14 %, H: 6.77 %, N: 3.25 %; Found C: 74.85 %, H: 6.72 %, N: 2.98 %.

## 例 29 : TZ315 の合成



3,5-ジ-tert-ブチルアニリン(X-1) 1.00 g (4.88 mmol)、4-ヨード安息香酸エチル 1.37 g (4.95 mmol)、*tert*-BuONa 549 mg (5.68 mmol) を無水トルエン 15 ml に溶かし、アルゴン置換下、トリス (ジベンジリデンアセトン) ジパラジウム(0) 91 mg、(R)-BINAP 139 mg (0.22 mmol) を入れ、100 °C で1時間攪拌した。室温まで冷やした後、エーテルで抽出した。有機層を食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮後、シリカゲルカラムクロマトグラフィー(酢酸エチル:n-ヘキサン= 1 : 6)で精製して、化合物 X-2 を 0.94 g (55%) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 7.92 (d, 2 H, J = 8.8 Hz), 7.14 (t, 1 H, J = 1.8 Hz), 7.02 (d, 2 H, J = 1.8 Hz), 6.96 (d, 2 H, J = 8.8 Hz), 4.33 (q, 2 H, J = 7.3 Hz), 1.37 (t, 3 H, J = 7.3 Hz), 1.32 (s, 18 H).

化合物 X-2 935 mg (2.65 mmol) を無水ベンゼン 10 ml に溶かし、アセチルク

ロライド 249 mg (3.18 mmol)、無水ピリジン 0.5 ml を加え、室温で5時間攪拌した。反応液に氷水を加え、酢酸エチルで抽出した。有機層を、希塩酸、食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮後、シリカゲルカラムクロマトグラフィー（酢酸エチル：n-ヘキサン＝ 1：4）で精製して、化合物 X-3 を 956 mg (92%) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 7.99 (d, 2 H, J = 8.4 Hz), 7.39 (s, 1 H), 7.34 (d, 2 H, J = 8.8 Hz), 7.05 (d, 2 H, J = 1.8 Hz), 4.35 (q, 2 H, J = 7.3 Hz), 2.04 (s, 3 H), 1.37 (t, 1 H, J = 7.0 Hz), 1.30 (s, 18 H).

化合物 X-3 950 mg (2.40 mmol) をアルゴン置換下、THF 8 ml にとかし、-78 °C にて攪拌しながら DIBAL 7.2 ml (1 M トルエン溶液、7.20 mmol) を徐々に滴下した。15 分後、反応液を 2 N 塩酸に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮した後、シリカゲルカラムクロマトグラフィー（酢酸エチル：n-ヘキサン＝ 1：2）で精製して、化合物 X-4 を 412 mg (55%) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 7.27 (m, 3 H), 7.04 (m, 3 H), 6.96 (d, 2 H, J = 1.5 Hz), 4.61 (s, 2 H), 1.31 (s, 18 H).

化合物 X-4 400 mg (1.29 mmol) をメタノールフリー塩化メチレン 8 ml に溶かし、活性 MnO<sub>2</sub> 1.32 g (85 %、12.9 mmol) を加え、室温で 12 時間攪拌した。反応液を濾過した後、濾液を濃縮し、シリカゲルカラムクロマトグラフィー（酢酸エチル：n-ヘキサン＝ 1：8 ついで 1：4）で精製して、化合物 X-5 を 184 mg (46%) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 9.78 (s, 1 H), 7.74 (d, 2 H, J = 8.8 Hz), 7.20 (t, 1 H, J = 1.8 Hz), 7.05 (d, 1 H, J = 1.8 Hz), 6.99 (d, 2 H, J = 8.4 Hz), 6.17 (s, 1 H), 1.33 (s, 18 H).

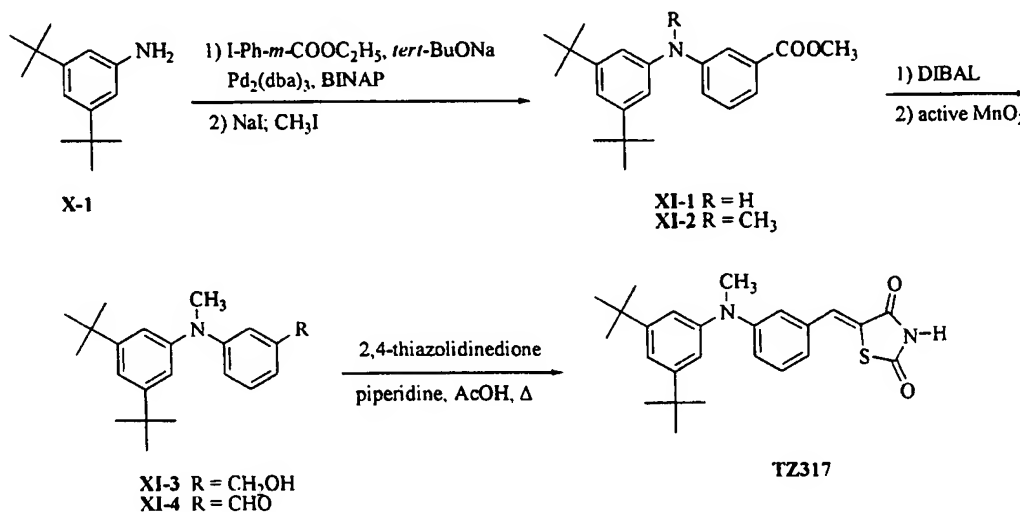
NaH 34 mg (60%, 0.87 mmol) を n-ヘキサンで洗い、DMF 1 ml に懸濁した。化合物 X-5 180 mg (0.58 mmol) を DMF 5 ml に溶かして加え、室温で 15 分攪拌した。この混合物に CH<sub>3</sub>I 0.14 ml (2.25 mmol) を加え更に 1 時間攪拌した。DMF を留去し、残渣に水を加え、塩化メチレンで抽出した。有機層を食塩水で洗い、

MgSO<sub>4</sub> で脱水、濃縮後、シリカゲルカラムクロマトグラフィー（酢酸エチル：n-ヘキサン = 1 : 6）で精製して、化合物 X-6 を 173 mg (92%) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 9.75 (s, 1 H), 7.68 (d, 2 H, J = 8.8 Hz), 7.33 (t, 1 H, J = 1.8 Hz), 7.05 (d, 2 H, J = 1.8 Hz), 6.74 (d, 2 H, J = 8.8 Hz), 3.40 (s, 3 H), 1.33 (s, 18 H).

化合物 X-6 170 mg (0.53 mmol) および 2,4-チアゾリジンジオン 62 mg (0.53 mmol) を無水トルエン 4 ml に懸濁し、ピペリジン 13.4 mg (0.16 mmol) と酢酸 9.5 mg (0.16 mmol) を無水トルエン 1.6 ml に溶解した溶液を加えて 120 °C にて 1.5 時間還流した。反応液を氷水に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮後、シリカゲルカラムクロマトグラフィー（酢酸エチル：n-ヘキサン = 1 : 3）で精製して、TZ315 を 197 mg (89%) 得た。TZ315 : Yellow needles (酢酸エチル/n-ヘキサン); mp 254 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 8.11 (br s, 1 H), 7.77 (s, 1 H), 7.34 (m, 3 H), 7.04 (d, 1 H, J = 1.8 Hz), 6.77 (d, 2 H, J = 8.8 Hz), 3.39 (s, 3 H), 1.33 (s, 18 H); Anal. Calcd. for C<sub>25</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>S, C: 71.06%, H: 7.16%, N: 6.63%; Found C: 70.96 %, H: 7.17 %, N: 6.81 %.

### 例 30 : TZ317 の合成



3-ヨード安息香酸メチル 1.37 g (5.23 mmol)、3,5-ジ-tert-ブチルアニリン (X-1) 1.00 g (4.88 mmol)、tert-BuONa 549 mg (5.68 mmol) を無水トルエン 15 ml に溶かし、アルゴン置換下、トリス (ジベンジリデンアセトン) ジパラジウム(0) 91 mg、(R)-BINAP 139 mg (0.22 mmol) を入れ、80℃で1時間撹拌した。室温まで冷やした後、エーテルで抽出した。有機層を食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮後、シリカゲルカラムクロマトグラフィー (酢酸エチル:n-ヘキサン = 1:8) で精製して、化合物 XI-1 (粗生成物) を 514 mg (31 %) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 7.87 (d, 1 H, J = 7.7 Hz), 7.75 (m, 1 H), 7.53 (m, 1 H), 7.29 (t, 1 H, J = 7.7 Hz), 7.07 (t, 1 H, J = 1.5 Hz), 6.98 (d, 2 H, J = 1.5 Hz), 3.88 (s, 3 H), 1.32 (s, 18 H).

NaH 88 mg (60 %, 2.21 mmol) を n-ヘキサンで洗い、DMF 1 ml に懸濁した。化合物 XI-1 (粗生成物) 500 mg (1.47 mmol) を DMF 8 ml に溶かして加え、室温で 15 分撹拌した。ヨウ化メチル 0.35 ml (5.62 mmol) を加えて 3 時間撹拌した。DMF を留去し、残渣に水を加えて塩化メチレンで抽出した。有機層を食塩水で洗う。MgSO<sub>4</sub> で脱水、溶媒留去した後、残渣をシリカゲルカラムクロマトグラフィー (酢酸エチル:n-ヘキサン = 1:10) で精製して、化合物 XI-2 を 180 mg (34.5 %) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 7.60 (m, 1 H), 7.47 (d, 1 H, J = 7.7 Hz), 7.23 (t, 1 H, J = 8.0 Hz), 7.17 (t, 1 H, J = 1.8 Hz), 7.04 (m, 1 H), 6.99 (d, 2 H, J = 1.8 Hz), 3.92 (s, 3 H), 3.88 (s, 3 H), 1.30 (s, 18 H).

化合物 XI-2 170 mg (0.48 mmol) をアルゴン置換下、THF 4 ml にとかし、-78 °C にて撹拌しながら DIBAL 1.44 ml (1 M トルエン溶液、1.44 mmol) を徐々に滴下した。30 分後、2 N 塩酸に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、MgSO<sub>4</sub> で脱水、溶媒を濃縮した。残渣をシリカゲルカラムクロマトグラフィー (酢酸エチル:n-ヘキサン = 1:3) で精製して、化合物 XI-3 を 130 mg (83 %) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 7.20 (t, 1 H, J = 1.8 Hz), 7.14 (t, 1 H, J = 1.8 Hz),

6.98 (d, 2 H,  $J = 1.8$  Hz), 6.92 (s, 1 H), 6.81 (d, 2 H,  $J = 8.1$  Hz), 4.62 (d, 2 H,  $J = 5.9$  Hz), 3.34 (s, 3 H), 1.30 (s, 18 H).

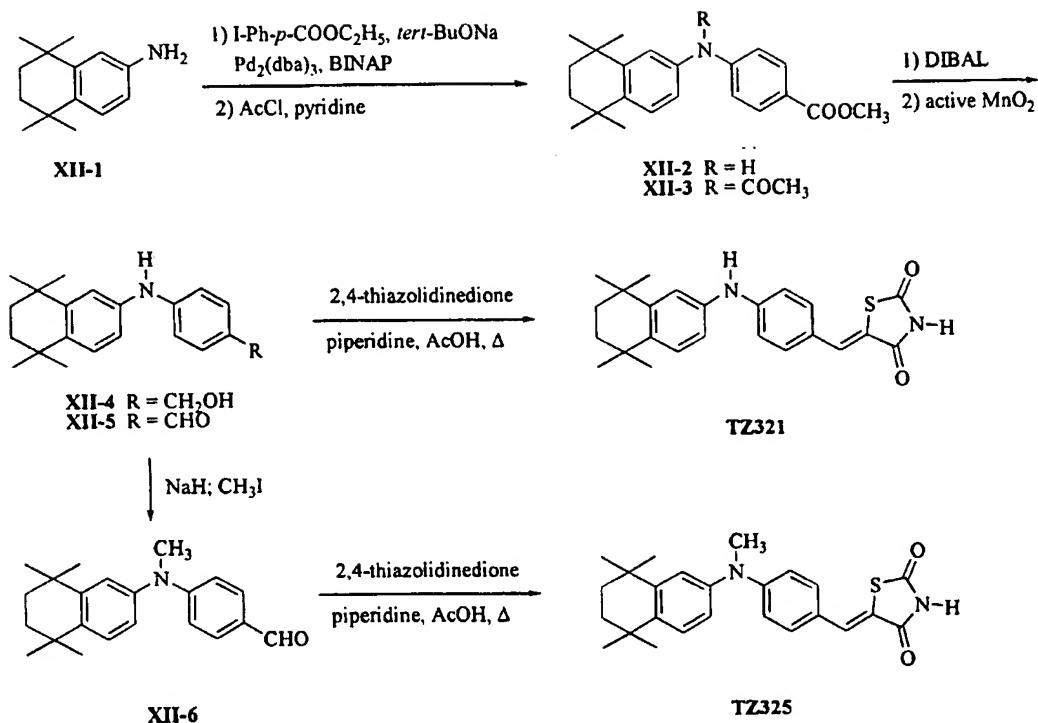
化合物 XI-3 125 mg (0.38 mmol) をメタノールフリー塩化メチレン 4 ml に溶かし、活性  $\text{MnO}_2$  394 mg (85 %、3.85 mmol) を加え、室温で 6.5 時間攪拌した。反応液を濾過し、濾液を濃縮した後、シリカゲルカラムクロマトグラフィー (酢酸エチル : *n*-ヘキサン = 1 : 6) で精製して、化合物 XI-4 を 43.5 mg (35 %) 得た (XI-3 を 51 mg 回収)。

$^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ ) 9.92 (s, 1 H), 7.35 (m, 1 H), 7.32 (t, 1 H,  $J = 7.7$  Hz), 7.27 (m, 1 H), 7.23 (t, 1 H,  $J = 1.8$  Hz), 7.07 (m, 1 H), 7.02 (d, 1 H,  $J = 1.8$  Hz), 3.37 (s, 3 H), 1.31 (s, 18 H).

化合物 XI-4 65 mg (0.20 mmol)、2,4-チアゾリジンジオン 23 mg (0.20 mmol) を無水トルエン 3 ml に懸濁した。ピペリジン 5.1 mg (0.060 mmol)、酢酸 3.6 mg (0.060 mmol) を無水トルエン 0.6 ml に溶解した溶液を加え 120°C で 3.5 時間還流した。反応液を氷水に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、 $\text{MgSO}_4$  で脱水、溶媒を濃縮した。残査をシリカゲルカラムクロマトグラフィー (酢酸エチル : *n*-ヘキサン = 1 : 2) で精製して、TZ317 を 88 mg (定量的) 得た。

TZ317 : Yellow needles (酢酸エチル/*n*-ヘキサン); mp 234 °C;  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ ) 8.41 (br s, 1 H), 7.77 (s, 1 H), 7.22-7.57 (m, 2 H), 7.01 (d, 2 H,  $J = 1.5$  Hz), 6.89 (dd, 2 H,  $J = 8.1, 2.2$  Hz), 6.83 (t, 1 H,  $J = 1.6$  Hz), 3.35 (s, 3 H), 1.32 (s, 18 H); Anal. Calcd. for  $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_2\text{S}$ , C: 71.06%, H: 7.16%, N: 6.63%; Found C: 70.88 %, H: 7.09 %, N: 6.36 %.

## 例 31 : TZ321 の合成



2-アミノ-5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチルナフタレン (XII-1) 1.50 g (7.39 mmol)、4-ヨード安息香酸エチル 1.70 g (6.16 mmol)、*tert*-BuONa 0.83 g (8.62 mmol) を無水トルエン 30 ml に溶かし、アルゴン置換下、トリス (ジベンジリデンアセトン) ジパラジウム(0) 138 mg (0.15 mmol) 及び (R)-BINAP 210 mg (0.33 mmol) をこの混合物に加えて 80℃で攪拌した。1時間後、反応液を室温まで冷やし、エーテルで抽出し、有機層を食塩水で洗浄した。MgSO<sub>4</sub> で脱水、濃縮した後、シリカゲルカラムクロマトグラフィー (酢酸エチル : *n*-ヘキサン = 1 : 8) で精製して、化合物 XII-2 を 1.38 g (64%) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 7.90 (d, 2 H, J = 8.8 Hz), 7.26 (d, 2 H, J = 8.4 Hz), 7.10 (d, 1 H, J = 2.5 Hz), 6.96 (dd, 1 H, J = 8.4, 2.6 Hz), 6.93 (d, 2 H, J = 8.8 Hz), 4.33 (q, 2 H, J = 7.0 Hz), 1.69 (s, 4 H), 1.37 (t, 3 H, J = 7.0 Hz), 1.28 (s, 6 H), 1.27 (s, 6 H)。

化合物 XII-2 1.95 g (5.56 mmol) を無水ピリジン 10 ml に溶かし、アセチルクロライド 523 mg (6.67 mmol) を加え、室温で 3 時間攪拌した。氷水を加え、酢酸エチルで抽出し、有機層を希塩酸、食塩水で洗浄した。MgSO<sub>4</sub> で脱水、濃縮した後、シリカゲルカラムクロマトグラフィー（酢酸エチル：n-ヘキサン = 1 : 3）で精製して化合物 XII-3 を 1.34 g (61.5%) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 8.00 (d, 2 H, J = 8.4 Hz), 7.32 (d, 2 H, J = 8.8 Hz), 7.31 (d, 1 H, J = 8.8 Hz), 7.14 (d, 1 H, J = 2.2 Hz), 6.95 (dd, 1 H, J = 8.4, 2.2 Hz), 4.35 (q, 2 H, J = 6.9 Hz), 2.05 (s, 3 H), 1.69 (s, 4 H), 1.37 (t, 3 H, J = 6.9 Hz), 1.28 (s, 6 H), 1.24 (s, 6 H).

化合物 XII-3 1.34 g (3.41 mmol) を THF 6 ml に溶かし、-78 °C にて DIBAL 10.2 ml (1.0 M トルエン溶液、10.2 mmol) を徐々に加えた。1 時間後、1 N 塩酸に注ぎ込み、酢酸エチルで抽出した。有機層を MgSO<sub>4</sub> で脱水、濃縮後、シリカゲルカラムクロマトグラフィー（酢酸エチル：n-ヘキサン = 1 : 2）で精製して、化合物 XII-4 を 621 mg (59%) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 7.24 (d, 2 H, J = 8.4 Hz), 7.03 (d, 1 H, J = 2.2 Hz), 7.00 (d, 2 H, J = 8.4 Hz), 6.89 (dd, 1 H, J = 8.4, 2.2 Hz), 4.60 (s, 2 H), 1.68 (s, 4 H), 1.27 (s, 6 H), 1.26 (s, 6 H).

化合物 XII-4 615 mg (2.0 mmol) をメタノールフリー塩化メチレン 8 ml に溶かし、活性 MnO<sub>2</sub> 2.05 g (85 %、20.0 mmol) を加え、室温で 16 時間攪拌した。反応液を濾過した後、濾液を濃縮、シリカゲルカラムクロマトグラフィー（酢酸エチル：n-ヘキサン = 1 : 4）で精製して化合物 XII-5 を 271 mg (44%) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 9.78 (s, 1 H), 7.73 (d, 2 H, J = 8.8 Hz), 7.29 (d, 1 H, J = 8.4 Hz), 7.11 (d, 1 H, J = 2.2 Hz), 6.99 (m, 3 H), 1.70 (s, 4 H), 1.29 (s, 6 H), 1.28 (s, 6 H).

化合物 XII-5 150 mg (0.49 mmol) および 2,4-チアゾリジンジオン 63 mg (0.54 mmol) を無水トルエン 6 ml に懸濁し、ピペリジン 12.7 mg (0.15 mmol) と酢酸 8.9 mg (0.15 mmol) を無水トルエン 1.5 ml に溶解した溶液を加えて 120 °C

にて 30 分還流した。反応液を氷水に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、 $\text{MgSO}_4$  で脱水、濃縮して TZ321 を 178 mg (90%) 得た。

TZ321 : Orange needles (酢酸エチル/*n*-ヘキサン); mp 297 °C;  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ , 30°C) 8.69 (s, 1 H), 7.65 (s, 1 H), 7.42 (d, 2 H,  $J = 8.8$  Hz), 7.26 (d, 1 H,  $J = 8.8$  Hz), 7.07 (d, 1 H,  $J = 2.6$  Hz), 7.06 (d, 2 H,  $J = 8.4$  Hz), 6.98 (dd, 1 H,  $J = 8.4, 2.6$  Hz), 1.64 (s, 4 H), 1.24 (s, 6H), 1.24 (s, 6 H), Anal. Calcd. for  $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_2\text{S}$ , C: 70.91 %, H: 6.45 %, N: 6.89 %; Found, C: 71.06 %, H: 6.42 %, N: 6.88 %.

#### 例 32 : TZ325 の合成

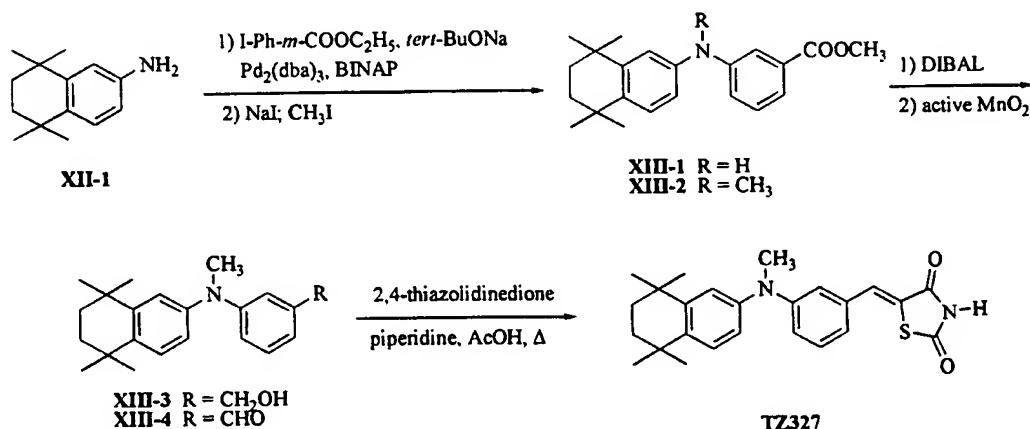
NaH 20 mg (60%, 0.49 mmol)を少量の *n*-ヘキサンで洗い、DMF 1 ml に懸濁した。この懸濁液に化合物 XII-5 100 mg (0.33 mmol) を 4 ml の DMF に溶かして加え、室温で 20 分攪拌した。この混合物に  $\text{CH}_3\text{I}$  0.08 ml (1.28 mmol)を加え、30 分攪拌した。DMF を減圧留去し、残渣に水を加えて塩化メチレンで抽出した。有機層を食塩水で洗い、 $\text{MgSO}_4$  で脱水、濃縮後、シリカゲルカラムクロマトグラフィー (酢酸エチル : *n*-ヘキサン = 1 : 5)で精製して、化合物 XII-6 を 80 mg (76.5%)得た。

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 9.75 (s, 1 H), 7.68 (d, 2 H,  $J = 9.2$  Hz), 7.34 (d, 1 H,  $J = 8.4$  Hz), 7.14 (d, 1 H,  $J = 2.2$  Hz), 6.96 (dd, 1 H,  $J = 8.4, 2.2$  Hz), 6.76 (d, 2 H,  $J = 9.2$  Hz), 3.37 (s, 3 H), 1.71 (s, 4 H), 1.31 (s, 6 H), 1.26 (s, 6 H).

化合物 XII-6 75 mg (0.23 mmol)、2,4-チアゾリジンジオン 30 mg (0.26 mmol) を無水トルエン 4 ml に懸濁し、ピペリジン 6.0 mg (0.07 mmol) と酢酸 12 mg (0.07 mmol)を無水トルエン 0.75 ml に溶解した溶液を加えて 120°Cにて還流した。30 分後、反応液を氷水に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、 $\text{MgSO}_4$  で脱水、濃縮後、シリカゲルカラムクロマトグラフィー (酢酸エチル : *n*-ヘキサン = 1 : 2)で精製して、TZ325 を 105 mg (定量的) 得た。

TZ325 : Yellow powder (酢酸エチル/n-ヘキサン); mp 238 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 8.29 (s, 1 H), 7.77 (s, 1 H), 7.33 (d, 2 H, J = 8.2 Hz), 7.33 (d, 1 H, J = 8.4 Hz), 7.13 (d, 1 H, J = 2.6 Hz), 6.95 (dd, 1 H, J = 8.4, 2.6 Hz), 6.79 (d, 2 H, J = 8.8 Hz), 3.36 (s, 3 H), 1.71 (s, 4 H), 1.31 (s, 6 H), 1.26 (s, 6 H), Anal. Calcd. for C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S, C: 71.40 %, H: 6.71 %, N: 6.66 %; Found, C: 71.51 %, H: 6.70 %, N: 6.60 %.

### 例 33 : TZ327 の合成



3-ヨード安息香酸メチル 1.24 g (4.73 mmol)、5,6,7,8-テトラヒドロ-5,5,8,8-テトラメチル-2-ナフチルアミン 1.03 g (5.07 mmol)、tert-BuONa 571 mg (5.92 mmol) を無水トルエン 30 ml に溶かし、アルゴン置換下、トリス (ジベンジリデンアセトン) ジパラジウム(0) 117 mg (0.13 mmol)、(R)-BINAP 177 mg (0.28 mmol) を入れ、80°Cで1時間攪拌した。反応液を室温まで冷やし、エーテルで抽出した。有機層を食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮後、シリカゲルカラムクロマトグラフィー (酢酸エチル : n-ヘキサン = 1 : 8) で精製して、化合物 XIII-1 を 877 mg (55%) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 7.70 (t, 1 H, 2.0 Hz), 7.50 (d, 1 H, J = 7.7 Hz),

7.28 (t, 1 H,  $J = 7.9$  Hz), 7.23 (d, 1 H,  $J = 8.4$  Hz), 7.17 (dd, 1 H,  $J = 8.1, 1.5$  Hz), 7.06 (d, 1 H,  $J = 2.2$  Hz), 6.90 (dd, 1 H,  $J = 8.4, 2.2$  Hz), 3.89 (s, 3 H), 1.69 (s, 4 H), 1.28 (s, 6 H), 1.27 (s, 6 H).

NaH 72 mg (60%, 1.78 mmol)を *n*-ヘキサンで洗い乾燥、DMF 1 ml に懸濁し、化合物 XIII-1 400 mg (1.19 mmol)を DMF 10 ml に溶かして加え、室温で攪拌した。20 分後、ヨウ化メチル 0.28 ml (4.50 mmol)を加え、40 分攪拌した。DMF を留去し、水を加え塩化メチレンで抽出した。有機層を食塩水で洗い、溶媒留去後、シリカゲルカラムクロマトグラフィー (酢酸エチル : *n*-ヘキサン = 1 : 8)で精製して、化合物 XIII-2 を 371.5 mg (94.5 %)得た。

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 7.60 (t, 1 H, 2.0 Hz), 7.47 (d, 1 H, 7.7 Hz), 7.25 (d, 1 H, 8.4 Hz), 7.22 (d, 1 H, 7.7 Hz), 7.08 (d, 1 H, 2.6 Hz), 7.05 (dd, 1 H, 8.4, 2.7 Hz), 6.88 (dd, 1 H, 8.4 Hz, 2.6 Hz), 3.88 (s, 3 H), 3.33 (s, 3 H), 1.68 (s, 4 H), 1.29 (s, 6 H), 1.24 (s, 6 H).

化合物 XIII-2 570 mg (1.62 mmol)をアルゴン置換下で THF 7 ml に溶解し、この溶液を $-78^\circ\text{C}$ にて攪拌しながら DIBAL 4.87 ml (1 M トルエン溶液、4.87 mmol)を徐々に滴下した。30 分後、反応液を 2 N 塩酸に注ぎ込み、酢酸エチルで抽出した。有機層を 2 N 塩酸、飽和炭酸水素ナトリウム水溶液、食塩水で洗い、 $\text{MgSO}_4$ で脱水、濃縮した後、シリカゲルカラムクロマトグラフィー (酢酸エチル : *n*-ヘキサン = 1 : 4 ついで 1 : 3)で精製して、化合物 XIII-3 を 500 mg (91%) 得た。

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 7.23 (d, 1 H, 8.3 Hz), 7.19 (d, 1 H, 8.1 Hz), 7.06 (d, 1 H, 2.6 Hz), 6.94 (br, 1 H), 6.88 (dd, 1 H, 8.4, 2.2 Hz), 6.84 (m, 2 H), 4.62 (s, 2 H), 3.31 (s, 3 H), 1.68 (s, 4 H), 1.29 (s, 6 H), 1.24 (s, 6 H).

化合物 XIII-3 100 mg (0.30 mmol)をメタノールフリー塩化メチレン 4 ml に溶かし、活性  $\text{MnO}_2$  303 mg (85 %, 2.97 mmol)を加え、室温で 24 時間攪拌した。反応液を濾過し、濾液を濃縮した後、シリカゲルカラムクロマトグラフィー (酢酸エチル : *n*-ヘキサン = 1 : 9)で精製して、化合物 XIII-4 を 71.6 mg (72 %) 得た。

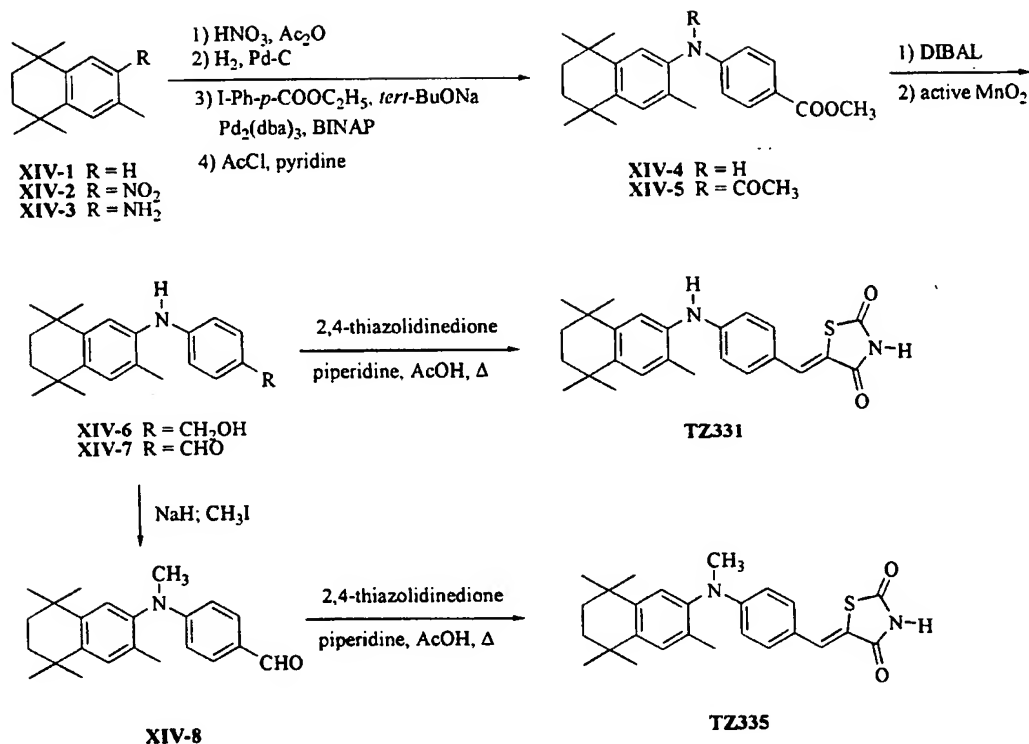
得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 9.92 (s, 1 H), 7.27–7.38 (m, 4 H), 7.10 (d, 1 H, 2.6 Hz), 7.06–7.09 (m, 1 H), 6.92 (dd, 1 H, 8.4, 2.2 Hz), 3.34 (s, 3 H), 1.69 (s, 4 H), 1.30 (s, 6 H), 1.24 (s, 6 H).

化合物 XIII-4 220 mg (0.66 mmol)、2,4-チアゾリジンジオン 84 mg (0.72 mmol) を無水トルエン 6 ml に懸濁し、ピペリジン 17 mg (0.20 mmol) と酢酸 12 mg (0.20 mmol) を無水トルエン 2 ml に溶解した溶液を加えて 120℃にて1時間還流した。反応液を氷水に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮後、シリカゲルカラムクロマトグラフィー（酢酸エチル：n-ヘキサン = 1：3）で精製して、TZ327 を 312 mg（定量的）得た。

TZ327 : Orange prisms（酢酸エチル／n-ヘキサン）; mp 196 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 8.39 (s, 3 H) 7.76 (s, 3 H) 7.31 (d, 1 H, 8.4 Hz) 7.27 (d, 1H, 8.4 Hz) 7.10 (d, 1 H, 2.2 Hz) 6.92 (dd, 1 H, 8.4 Hz, 2.2 Hz) 6.89 (d, 2 H, 7.0 Hz) 6.83 (t, 1 H, 2.0 Hz) 3.32 (s, 3 H) 1.71 (s, 4 H) 1.31 (s, 6 H) 1.26 (s, 6 H); Anal. Calcd. for C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S, C: 71.40 %, H: 6.71 %, N: 6.66 %; Found, C: 71.15 %, H: 6.61 %, N: 6.44 %.

## 例 34 : TZ331 の合成



1, 2, 3, 4-テトラヒドロ-1, 1, 4, 4, 6-ペンタメチルナフタレン 2.69 g (13.3 mmol) を無水酢酸 20 ml に溶かして 0 °C に冷却した。この溶液に 61 % 硝酸 0.74 ml (16.0 mmol) を徐々に加えた。2 時間後、反応液を氷水にあげ、水酸化ナトリウムで中和した後、エーテルで抽出した。有機層を食塩水で振り、 $\text{MgSO}_4$  で脱水後、濃縮して、化合物 XIV-2 を 3.03 g (92%) 得た。

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 7.96 (s, 1 H), 7.21 (s, 1 H), 2.56 (s, 3 H), 1.70 (s, 4 H), 1.30 (s, 6 H), 1.29 (s, 6 H)。

化合物 XIV-2 3.02 g (12.2 mmol) を酢酸エチル 20 ml、エタノール 30 ml に溶かし、Pd/C 400 mg を加えて室温で接触水素還元。6.5 時間後、触媒を濾過して除き、濾液を濃縮した。残渣をシリカゲルカラムクロマトグラフィー (酢酸エチル : n-ヘキサン = 1 : 4) で精製して、化合物 XIV-3 を 1.48 g (56%) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 6.97 (s, 1 H), 6.61 (s, 1 H), 3.45 (br s, 2 H), 2.14 (s, 3 H), 1.64 (s, 4 H), 1.24 (s, 6 H), 1.24 (s, 6 H).

4-ヨード安息香酸メチル 3.82 g (13.8 mmol)、化合物 XIV-3 3.00 g (13.8 mmol) および tert-BuONa 1.55 g (16.1 mmol) を無水トルエン 30 ml に溶かし、アルゴン置換下、トリス (ジベンジリデンアセトン) ジパラジウム(0) 320 mg (0.35 mmol)、(R)-BINAP 480 mg (0.77 mmol) を加えて 100 °C で 3 時間攪拌した。反応液を室温まで冷やし、エーテルで抽出した。有機層を食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮した後、シリカゲルカラムクロマトグラフィー (酢酸エチル:n-ヘキサン = 1:10) で精製して、化合物 XIV-4 を 2.04 g (40 %) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 7.89 (d, J = 8.8 Hz, 2 H), 7.21 (s, 1 H), 7.18 (s, 1 H), 6.76 (d, J = 8.8 Hz, 2 H), 4.32 (q, J = 7.0 Hz, 2 H), 2.19 (s, 3 H), 1.68 (s, 4 H), 1.37 (t, J = 7.0 Hz, 3 H), 1.29 (s, 6 H), 1.24 (s, 6 H).

化合物 XIV-4 2.03 g (5.56 mmol) を無水ベンゼン 30 ml に溶かし、アセチルクロライド 524 mg (6.67 mmol)、無水ピリジン 1 ml を加え、室温で 2 時間攪拌した。反応液にアセチルクロライド 0.20 ml を追加し、50 °C で 4 時間、更に 60 °C で 23 時間攪拌した。反応液に氷水を加え、酢酸エチルで抽出した。有機層を 2 N 塩酸および食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮した。残渣をシリカゲルカラムクロマトグラフィー (酢酸エチル:n-ヘキサン = 1:4) で精製して、化合物 XIV-5 を 1.66 g (62 %) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 7.97 (d, J = 8.8 Hz, 2 H), 7.33 (d, J = 8.8 Hz, 2 H), 7.17 (s, 1 H), 7.13 (s, 1 H), 4.34 (q, J = 7.0 Hz, 2 H), 2.06 (s, 3 H), 1.97 (s, 3 H), 1.69 (s, 4 H), 1.36 (t, J = 7.0 Hz, 3 H), 1.29 (s, 6 H), 1.26 (s, 6 H).

化合物 XIV-5 1.62 g (3.98 mmol) をアルゴン置換下で THF 10 ml に溶解し、この溶液を -78 °C にて攪拌しながら DIBAL 11.9 ml (1 M トルエン溶液、11.9 mmol) をゆっくり滴下した。30 分後、反応液を 2 N 塩酸に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮後、シリカゲルカラムクロ

マトグラフィー (酢酸エチル: n-ヘキサン = 1:2) で精製して、化合物 XIV-6 を 0.99 g (77 %) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 7.23 (d, J = 8.4 Hz, 2 H), 7.19 (s, 1 H), 7.12 (s, 1 H), 6.87 (d, J = 8.4 Hz, 2 H), 5.33 (s, 1 H), 4.60 (d, J = 5.5 Hz, 2 H), 2.20 (s, 3 H), 1.67 (s, 4 H), 1.51 (t, J = 5.6 Hz, 1 H), 1.28 (s, 6 H) 1.22 (s, 6 H).

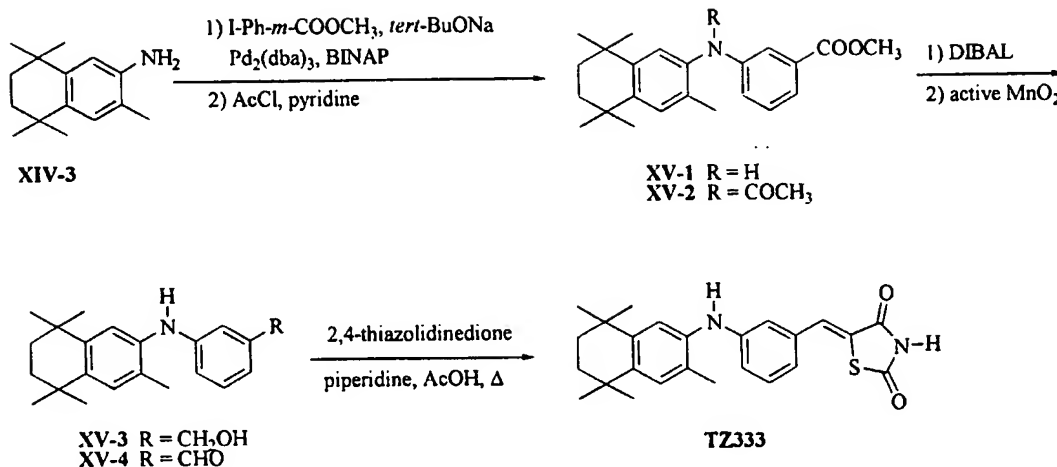
化合物 XIV-6 985 mg (3.05 mmol) をメタノールフリー塩化メチレン 14 ml に溶かし、活性 MnO<sub>2</sub> 3.11 g (85 %、30.5 mmol) を加え、室温で 22 時間攪拌した。反応液を濾過し、濾液を濃縮した後、シリカゲルカラムクロマトグラフィー (酢酸エチル: n-ヘキサン = 1:4) で精製して、化合物 XIV-6 を 297 mg (30 %、原料回収 282 mg) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 9.76 (s, 1 H), 7.71 (d, J = 8.8 Hz, 2 H), 7.20 (s, 1 H), 7.18 (s, 1 H), 6.78 (d, J = 8.4 Hz, 2 H), 5.80 (s, 1 H), 2.05 (s, 3 H), 1.69 (s, 4 H), 1.30 (s, 6 H), 1.25 (s, 6 H).

化合物 XIV-6 70 mg (0.22 mmol)、2,4-チアゾリジンジオン 25.5 mg (0.22 mmol) を無水トルエン 4 ml に懸濁し、ピペリジン 5.6 mg (0.065 mmol) と酢酸 3.9 mg (0.065 mmol) を無水トルエン 0.67 ml に溶解した溶液を加えて 120°C にて 7 時間還流した。反応液を氷水に注ぎ込み、酢酸エチルで抽出した。有機層を、食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮後、シリカゲルカラムクロマトグラフィー (酢酸エチル: n-ヘキサン = 1:2) で精製して、TZ331 を 72.5 mg (79 %) 得た。

TZ331 : Yellow needles (塩化メチレン/n-ヘキサン); mp 284 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 8.31 (br s, 1 H), 7.77 (s, 1 H), 7.36 (d, J = 8.8 Hz, 2 H), 7.19 (s, 1 H), 7.17 (s, 1 H), 6.81 (d, J = 8.8 Hz, 2 H), 5.74 (s, 1 H), 2.19 (s, 3 H), 1.69 (s, 4 H), 1.29 (s, 6 H), 1.25 (s, 6 H); Anal. Calcd. for C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S, C: 71.40 %, H: 6.71 %, N: 6.66 %.

## 例 35 : TZ333 の合成



3-ヨード安息香酸メチル 1.77 g (6.77 mmol)、化合物 XIV-3 1.47 g (6.77 mmol) および *tert*-BuONa 763 mg (7.91 mmol) を無水トルエン 15 ml に溶かし、アルゴン置換下、トリス (ジベンジリデンアセトン) ジパラジウム(0) 122 mg (0.14 mmol)、(R)-BINAP 187 mg (0.30 mmol) を加えて 100 °C で 2.5 時間撹拌した。反応液を室温まで冷やし、エーテルで抽出した。有機層を食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮後、シリカゲルカラムクロマトグラフィー (酢酸エチル : *n*-ヘキサン = 1 : 8) で精製して、化合物 XV-1 を 1.45 g (61 %) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 7.59 (t, *J* = 2.0 Hz, 1 H), 7.48 (td, *J* = 7.7, 1.2 Hz, 1 H), 7.27 (t, *J* = 7.8 Hz, 1 H), 7.20 (s, 1 H), 7.14 (s, 1 H), 7.04 (m, 1 H), 5.42 (br s, 1 H), 3.88 (s, 3 H), 2.19 (s, 3 H), 1.68 (s, 4 H), 1.29 (s, 6 H), 1.24 (s, 6 H)。

化合物 XV-1 1.44 g (4.10 mmol) を無水ベンゼン 16 ml に溶かし、アセチルクロライド 386 mg (4.92 mmol)、無水ピリジン 1 ml を加え、室温で 2 時間撹拌した。反応液にアセチルクロライド 0.20 ml を追加し、50 °C で 4 時間、更に 70 °C で 6 時間撹拌した。反応液に氷水を加え、酢酸エチルで抽出した。有機層を 2 N 塩酸および食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮した。残査をシリカゲルカラムク

ロマトグラフィー (酢酸エチル : n-ヘキサン = 1 : 2) で精製して、化合物 XV-2 を 1.37 g (85 %) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 8.00 (s, 1 H), 7.82 (br d, 1 H), 7.45 (td, J = 8.0, 2.2 Hz, 1 H), 7.37 (bt, J = 8.3 Hz, 1 H), 7.19 (br s, 1 H), 7.15 (s, 1 H), 3.88 (s, 3 H), 2.10 (s, 3 H), 1.96 (s, 3 H), 1.69 (s, 4 H), 1.27 (s, 12 H).

化合物 XV-2 1.37 g (3.49 mmol) をアルゴン置換下、THF 8 ml にとかし、-78 °C にて攪拌しながら DIBAL 10.5 ml (1 M トルエン溶液、10.5 mmol) をゆっくり滴下した。30 分後、反応液を 2 N 塩酸に注ぎ込み、酢酸エチルで抽出した。有機層を 2 N 塩酸および食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮後、シリカゲルカラムクロマトグラフィー (酢酸エチル : n-ヘキサン = 1 : 3) で精製して、化合物 XV-3 を 0.91 g (81 %) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 7.21 (t, J = 7.7 Hz, 1 H), 7.20 (s, 1 H), 7.12 (s, 1 H), 6.92 (s, 1 H), 6.82 (m, 2 H), 5.35 (br s, 1 H), 4.62 (d, J = 5.8 Hz, 2 H), 2.19 (s, 3 H), 1.68 (s, 4 H), 1.59 (t, J = 5.8 Hz, 1 H), 1.28 (s, 6 H), 1.23 (s, 6 H).

化合物 XV-3 900 mg (2.79 mmol) をメタノールフリー塩化メチレン 12 ml に溶かし、活性 MnO<sub>2</sub> 2.86 g (85 %、27.9 mmol) を加え、室温で 15 時間攪拌した。反応液を濾過し、濾液を濃縮した後、シリカゲルカラムクロマトグラフィー (酢酸エチル : n-ヘキサン = 1 : 8) で精製して、化合物 XV-4 を 119 mg (13 %) 得た。

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 9.92 (s, 1 H), 7.37 (t, J = 7.7 Hz, 1 H), 7.31 (m, 2 H), 7.18 (s, 1 H), 7.15 (s, 1 H), 7.09 (m, 1 H), 5.48 (br s, 1 H), 2.19 (s, 3 H), 1.68 (s, 4 H), 1.29 (s, 6 H), 1.24 (s, 6 H).

化合物 XV-4 115 mg (0.36 mmol)、2,4-チアゾリジンジオン 84 mg (0.72 mmol) を無水トルエン 8 ml に懸濁し、ピペリジン 9.2 mg (0.11 mmol) と酢酸 6.4 mg (0.11 mmol) を無水トルエン 1.1 ml に溶解した溶液を加えて 120 °C にて 7 時間還流した。反応液を氷水に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮後、シリカゲルカラムクロマトグラフィー (酢酸エチル : n-ヘキサン = 1 : 8) で精製して、化合物 XV-5 を 115 mg (100 %) 得た。

ル：n-ヘキサン＝ 1：2)で精製して、TZ333 を 138 mg (92 %)得た。

TZ333 : Yellow needles (酢酸エチル／n-ヘキサン); mp 223 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 8.29 (br s, 1 H), 7.75 (s, 1 H), 7.30 (t, J = 8.1 Hz, 1 H), 7.17 (s, 1 H), 7.15 (s, 1 H), 6.93 (m, 2 H), 6.81 (m, 1 H), 5.43 (s, 1H), 2.19 (s, 3 H), 1.69 (s, 4 H), 1.30 (s, 6 H), 1.24 (s, 6 H); Anal. Calcd. for C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S, C: 71.40 %, H: 6.71 %, N: 6.66 %; Found, C: 71.20%, H: 6.76 %, N: 6.65 %.

### 例 36 : TZ335 の合成

NaH 40 mg (60%, 1.01 mmol)を少量の n-ヘキサンで洗い、DMF 1 ml に懸濁した。この懸濁液に XIV-7 216 mg (0.67 mmol)を 6 ml の DMF に溶かして加え、室温で 20 分攪拌した。反応液に CH<sub>3</sub>I 0.08 ml (1.35 mmol)を加え、30 分攪拌した。DMF を減圧留去し、水を加えて塩化メチレンで抽出した。有機層を食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮後、シリカゲルカラムクロマトグラフィー (酢酸エチル：n-ヘキサン＝ 1：4)で精製して、XIV-8 を 140 mg (62 %)得た。

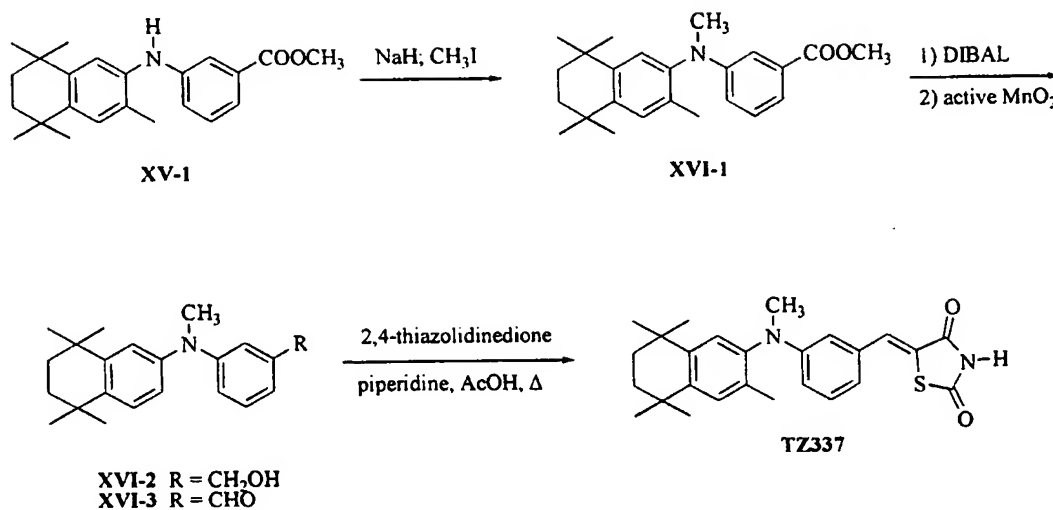
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 9.73 (s, 1 H), 7.67 (d, J = 8.1 Hz, 2 H), 7.20 (s, 1 H), 7.03 (s, 1 H), 6.54 (br s, 2 H), 3.30 (s, 3 H), 2.04 (s, 3 H), 1.69 (s, 4 H), 1.31 (s, 6 H), 1.23 (s, 6 H).

XIV-8 130 mg (0.39 mmol) 、2,4-チアゾリジンジオン 45 mg (0.39 mmol)を無水トルエン 6 ml に懸濁し、ピペリジン 9.9 mg (0.12 mmol) と酢酸 7 mg (0.12 mmol) を無水トルエン 1.2 ml に溶解した溶液を加えて 120°Cにて還流した。6 時間後、反応液を氷水に注ぎ込み、塩化メチレンで抽出した。有機層を食塩水で洗い、MgSO<sub>4</sub> で脱水、濃縮後、シリカゲルカラムクロマトグラフィー (酢酸エチル：n-ヘキサン＝ 1：3)で精製して、TZ335 を 145 mg (86 %)得た。

TZ335 : Yellow powder (塩化メチレン／メタノール); mp >300 °C; <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 12.30 (br s, 1 H), 7.63 (s, 1 H), 7.39 (d, J = 8.4 Hz, 2 H), 7.29 (s, 1 H), 7.09 (s, 1 H), 6.53 (d, J = 8.3 Hz, 2 H), 3.29 (s, 3 H), 1.99 (s, 3 H), 1.65 (s, 4 H), 1.27 (s, 6 H), 1.21 (s, 6 H), Anal. Calcd.

for  $C_{26}H_{30}N_2O_2S$ , C: 71.86 %, H: 6.96 %, N: 6.45 %; Found, C: 71.60 %, H: 6.99 %, N: 6.67 %.

例 37 : TZ337 の合成



NaH 146 mg (60%、3.65 mmol)を少量の *n*-ヘキサンで洗い、DMF 1 ml に懸濁した。この懸濁液に XV-1 855 mg (2.44 mmol)を 12 ml の DMF に溶かして加え、室温で 20 分攪拌した。反応液に  $\text{CH}_3\text{I}$  0.30 ml (4.87 mmol)を加え、1 時間攪拌した。DMF を減圧留去し、水を加えて塩化メチレンで抽出した。有機層を食塩水で洗い、 $\text{MgSO}_4$  で脱水、濃縮後、シリカゲルカラムクロマトグラフィー (酢酸エチル : *n*-ヘキサン = 1 : 10) で精製して、XVI-1 を 788.5 mg (89 %)得た。

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 7.34 (d,  $J = 7.7$  Hz, 1 H), 7.30 (m, 1 H), 7.17 (s, 1 H), 7.16 (t,  $J = 7.7$  Hz, 1 H), 7.04 (s, 1 H), 6.59 (dd,  $J = 7.4, 1.8$  Hz, 1 H), 3.88 (s, 3 H), 3.25 (s, 3 H), 2.04 (s, 3 H), 1.68 (s, 4 H), 1.30 (s, 3 H), 1.22 (s, 3 H).

XVI-1 750 mg (2.05 mmol) をアルゴン置換下、THF 7 ml にとかし、 $-78^\circ\text{C}$  にて攪拌しながら DIBAL 6.16 ml (1 M トルエン溶液、6.16 mmol)を徐々に滴下し

た。30 分後、反応液を 2 N 塩酸に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、 $\text{MgSO}_4$  で脱水、濃縮後、シリカゲルカラムクロマトグラフィー（酢酸エチル： $n$ -ヘキサン = 1 : 2）で精製して、XVI-2 を 616 mg (89%) 得た。

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 7.16 (s, 1 H), 7.14 (t,  $J = 7.7$  Hz, 1 H), 7.04 (s, 1 H), 6.68 (d,  $J = 7.3$  Hz, 1 H), 6.58 (s, 1H), 6.41 (dd,  $J = 8.1, 2.2$  Hz, 1 H), 4.60 (d,  $J = 5.8$  Hz, 2 H), 3.22 (s, 3 H), 2.06 (s, 3 H), 1.68 (s, 4 H), 1.52 (t,  $J = 5.9$  Hz, 1 H), 1.30 (s, 6 H), 1.21 (s, 6 H)。

XVI-2 610 mg (1.81 mmol) をメタノールフリー塩化メチレン 8 ml に溶かし、活性  $\text{MnO}_2$  1.85 g (85%, 18.1 mmol) を加え、室温で 30 時間攪拌した。反応液を濾過し、濾液を濃縮した後、シリカゲルカラムクロマトグラフィー（酢酸エチル： $n$ -ヘキサン = 1 : 10）で精製して、XV-3 を 423 mg (70%) 得た。

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 9.91 (s, 1 H), 7.28 (t,  $J = 7.3$  Hz, 1 H), 7.18 (m, 2 H), 7.07 (m, 1 H), 7.04 (s, 1 H), 6.69 (dd,  $J = 8.4, 2.6$  Hz, 1 H), 3.26 (s, 3 H), 2.05 (s, 3 H), 1.69 (s, 4 H), 1.31 (s, 6 H), 1.22 (s, 6 H)。

XV-3 415 mg (1.24 mmol)、2,4-チアゾリジンジオン 145 mg (1.42 mmol) を無水トルエン 10 ml に懸濁し、ピペリジン 32 mg (0.37 mmol) と酢酸 22 mg (0.37 mmol) を無水トルエン 4 ml に溶解した溶液を加えて 120°C にて還流した。6 時間後、反応液を氷水に注ぎ込み、酢酸エチルで抽出した。有機層を食塩水で洗い、 $\text{MgSO}_4$  で脱水、濃縮後、シリカゲルカラムクロマトグラフィー（酢酸エチル： $n$ -ヘキサン = 1 : 3）で精製して、TZ337 を 504 mg (94 %) 得た。

TZ337 : Orange crystals (酢酸エチル/ $n$ -ヘキサン); mp 219 °C;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 8.22 (br s, 1 H), 7.74 (s, 1 H), 7.27 (t,  $J = 7.7$  Hz, 1 H), 7.04 (s, 1 H), 6.80 (d,  $J = 8.4$  Hz, 1 H), 6.64 (dd,  $J = 8.0, 2.2$  Hz, 1H), 6.48 (s, 1 H), 3.26 (s, 3 H), 2.05 (s, 3 H), 1.70 (s, 4 H), 1.32 (s, 6 H), 1.24 (s, 6 H); Anal. Calcd. for  $\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_2\text{S}$ , C: 71.86 %, H: 6.96%, N: 6.45 %; Found, C: 71.65 %, H: 7.16 %, N: 6.75 %。

## 例 38 : 試験例

本発明の各化合物を用いて、単独での細胞分化誘導作用および共存するレチノイドの細胞分化誘導作用に対する効果を検討した。比較および共存させるレチノイドとして Am80 [4-[(5,6,7,8- テトラヒドロ-5,5,8,8- テトラメチル-2- ナフトアレニル) カルバモイル] 安息香酸を用いた。前骨髄球性白血病細胞株 HL-60 を用いて、顆粒球系への分化を、形態変化およびニトロブルーテトラゾリウム (NBT) の還元能測定により判定した。以下の表に示した分化した細胞の割合 (%) は NBT 還元能から算出したものである。

(A) 各化合物単独の濃度依存的分化誘導能および  $1 \times 10^{-9}$  M Am80 の分化誘導能に対する濃度依存的効果を測定した。TZ91 および TZ181 は単独でも細胞分化誘導活性を示し、さらに細胞分化誘導活性を示さない濃度において共存する Am80 の活性を増強していた。また、TZ201 はそれ自身では活性を持たないが、共存する Am80 の活性を抑制していた。

表 1

化合物	化合物単独での分化誘導した細胞の割合 (%)				1×10 <sup>-9</sup> M Am80 と共存した場合の分化誘導した細胞の割合 (%)				
	濃 度				濃 度				
	-9	-8	-7	-6	none	-9	-8	-7	-6
<b>TZ91</b>	1.2	0.8	7	87	49	58	62	87	-
<b>TZ181</b>	-	1	7	54	37	-	53	58	6
<b>TZ201</b>	-	0.3	0.7	0.3	48	-	64	53	5

(B) 各化合物単独の濃度依存的分化誘導能および  $1 \times 10^{-10}$  M Am80 の分化誘導能に対する濃度依存的効果を測定した。TZ151 は単独でも細胞分化誘導活性を示し、さらに細胞分化誘導活性を示さない濃度において共存する Am80 の活性を増強していた。また、TZ161 および TZ191 はそれ自身では活性を持たないが、共存する Am80 の活性を増強しており、高濃度 ( $1 \times 10^{-6}$  M) では抑制的に作用していた。

表 2

化合物	化合物単独での分化誘導した 細胞の割合 (%)			1×10 <sup>-10</sup> M Am80 と共存した場合の 分化誘導した細胞の割合 (%)			
	濃 度			濃 度			
	-8	-7	-6	none	-8	-7	-6
<b>TZ151</b>	3	4.4	78	4	12	43	83
<b>TZ161</b>	3.5	1.8	3.6	4	12	25	3.8
<b>TZ191</b>	3.6	3.5	4.1	11	63	75	28

(C) 各化合物単独の濃度依存的分化誘導能および 3×10<sup>-9</sup> M Am80 の分化誘導能に対する濃度依存的効果を測定した。上記 5 化合物のうち TZ241 以外の化合物は単独でも細胞分化誘導活性を示し、さらに 5 つ全ての化合物について細胞分化誘導活性を示さない濃度で共存する Am80 の活性増強が認められた。

表 3

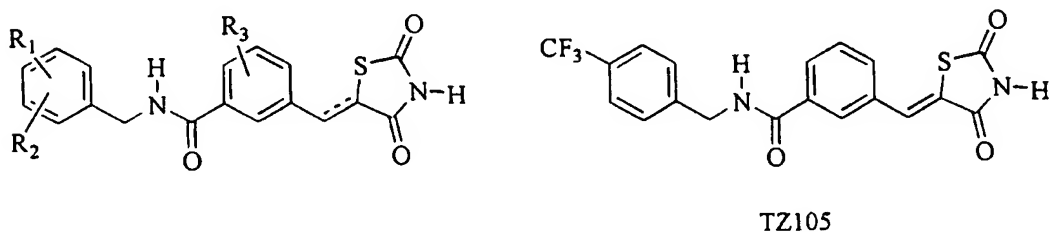
化合物	化合物単独での分化誘導した 細胞の割合 (%)				3×10 <sup>-9</sup> M Am80 と共存した場合の 分化誘導した細胞の割合 (%)		
	濃 度				濃 度		
	-8	-7	-6	none	-8	-7	-6
<b>TZ221</b>	1.4	2	51	44	54	67	82
<b>TZ241</b>	2.8	6.4	89	44	76	84	92
<b>TZ245</b>	3.8	3	11	44	86	89	88
<b>TZ321</b>	1.2	1.1	28	51	55	83	88
<b>TZ325</b>	2.2	21	87	51	72	83	79

(D) 各化合物の濃度を 1×10<sup>-6</sup> M に固定して、レチノイド (Am80) の濃度依存的分化誘導能に対する効果を測定した。上記 4 化合物は単独では細胞分化誘導活性を示さず、共存する Am80 の活性を抑制していた。

表 4

化合物	共存レチノイド (濃度)			
	none	Am80(-9)	Am80(-9.5)	Am80(-10)
none	1.5	80	53	8.5
<b>TZ223</b>	4.4	62	22	5
<b>TZ227</b>	5.3	11.7	5.5	7
<b>TZ243</b>	4.2	77	35	5
<b>TZ247</b>	7	10	5.8	6.4

(E) 特開平 9-48771 には、下記一般式で示される N-ベンジルジオキソチアゾリジルベンズアミド誘導体がインスリン抵抗性改善作用を有することが示されている。そこで、比較のために N-ベンジル誘導体として TZ105 を合成し、レチノイド活性の有無を検討した。



II-2 (例 4 参照) 150 mg (0.60 mmol) を無水ベンゼン 12 ml に懸濁し、 $\text{SOCl}_2$  358 mg (3.01 mmol) を加えて 14 時間還流した。 $\text{SOCl}_2$  を留去した後、残渣を無水ベンゼン 10 ml に懸濁し、4-トリフルオロベンジルアミン 106 mg (0.60 mmol)、無水ピリジン 1 ml を加えて室温で 1 時間攪拌した。反応液に氷を浮かべた 2 N 塩酸を加え、酢酸エチルで抽出した。有機層を食塩水で洗い、 $\text{MgSO}_4$  で脱水、濃縮した後、シリカゲルカラムクロマトグラフィー (酢酸エチル:n-ヘキサン = 3:2) で精製して TZ105 を 128 mg (52 %) 得た。

TZ105 : Colorless needles (酢酸エチル/n-ヘキサン); mp 204 °C; <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30 °C) 9.23 (t, 1 H, J = 5.9 Hz), 8.10 (s, 1 H), 7.97 (d, 1

H,  $J = 8.7$  Hz), 7.83 (s, 1 H), 7.76 (d, 1 H,  $J = 8.7$  Hz), 7.70 (d, 2 H,  $J = 8.1$  Hz), 7.65 (t, 1 H,  $J = 7.7$  Hz), 7.55 (d, 2 H,  $J = 8.0$  Hz), 4.59 (d, 2 H,  $J = 5.9$  Hz); Anal. Calcd. for  $C_{19}H_{13}N_2O_3SF_3$ , C: 56.16 %, H: 3.22 %, N: 6.89 %, Found C: 56.36 %, H: 3.04 %, N: 6.98 %.

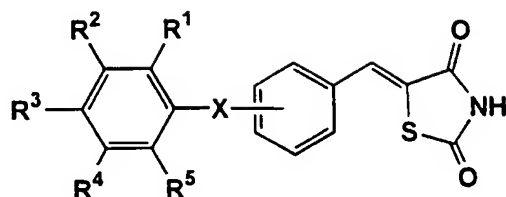
前述した HL-60 細胞を用いた検定系において、TZ105 は全く分化誘導活性を示さず、また、共存するレチノイド Am80 の作用にも影響を及ぼさなかった。従って、N-ベンジル体ではレチノイドもしくはレチノイド制御作用は発揮されず、この骨格においては TZ185 等のように窒素原子上の芳香環の存在が必須であると考えられる。

#### 産業上の利用可能性

本発明の化合物は、レチノイドレセプターに作用してレチノイド様作用やその調節作用（レチノイドの作用増強又は作用抑制）などを発揮するので、例えば癌、糖尿病、動脈硬化症、骨疾患、リウマチ、又は免疫性疾患などの疾患の予防及び／又は治療のための医薬の有効成分として有用である。

## 請 求 の 範 囲

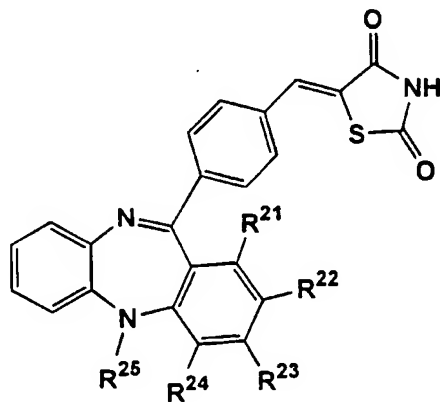
## 1. 下記的一般式(I):



〔式中、 $R^1$ 、 $R^2$ 、 $R^3$ 、 $R^4$ 、及び  $R^5$  はそれぞれ独立に水素原子又は低級アルキル基を示し、それらのうちの隣接する2つの基は一緒になってそれらが結合するフェニル環上の炭素原子とともに1又は2以上アルキル基を有することもある5員環又は6員環を形成してもよく；Xは $-C(R^6)=CH-$ 、 $-CH=C(R^7)-$ 、 $-N(R^8)-CO-$ 、 $-CO-N(R^9)-$ 、 $-C(=CHR^{10})-$ 、 $-CO-$ 、又は $-NR^{11}-$ で表される基（式中、 $R^6$ 、 $R^7$ 、 $R^8$ 、 $R^9$ 、 $R^{10}$ 、及び $R^{11}$ はそれぞれ独立に水素原子又は低級アルキル基を示す）を示す〕

で表される化合物；若しくは

## 下記的一般式(II)：



〔式中、 $R^{21}$ 、 $R^{22}$ 、 $R^{23}$ 、及び  $R^{24}$  はそれぞれ独立に水素原子又は低級アルキル基を示し、それらのうちの隣接する2つの基は一緒になってそれらが結合するフ

フェニル環上の炭素原子とともに1又は2以上のアルキル基を有することもある5員環又は6員環を形成してもよく；R<sup>25</sup>は水素原子又は低級アルキル基を示す]で表される化合物、又はそれらの塩。

2. 請求の範囲第1項に記載の式(I)又は式(II)の化合物及び生理学的に許容されるそれらの塩、並びにそれらの水和物及び溶媒和物からなる群から選ばれる物質を有効成分として含む医薬。

3. レチノイドレセプター作用剤である請求の範囲第2項に記載の医薬。

4. レチノイドの作用を増強する作用を有する請求の範囲第2項又は第3項に記載の医薬。

5. レチノイドの作用を抑制する作用を有する請求の範囲第2項又は第3項に記載の調節剤。

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/05091

## A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl<sup>6</sup> C07D277/34, 417/10, A61K31/425, 31/55

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl<sup>6</sup> C07D277/34, 417/10, A61K31/425, 31/55

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS (STN), REGISTRY (STN), WPIDS (STN), MEDLINE (STN)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, 97/11061, A1 (Nikken Chemicals Co., Ltd.), 27 March, 1997 (27. 03. 97) & CA, 2233012, A & NO, 9801269, A & AU, 9670015, A1 & JP, 10-59951, A2	1-5
A	JP, 7-17854, A (Hoechst Japan Ltd.), 20 January, 1995 (20. 01. 95) & EP, 619116, A2 & CA, 2120424, AA & US, 5525618, A & US, 5716995, A & US, 5703128, A & US, 5767146, A	1-5
PX	EBISAWA, M., et al., "NOVEL THIAZOLIDINEDIONE DERIVATIVES WITH RETINOID SYNERGENIC ACTIVITY", Biol. Pharm. Bull., 21(5), May 1998, pp.547-549	1-4
PA		5

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date  
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search  
18 January, 1999 (18. 01. 99)Date of mailing of the international search report  
26 January, 1999 (26. 01. 99)Name and mailing address of the ISA/  
Japanese Patent Office

Authorized officer

Facsimile No.

Telephone No.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/05091

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Regarding the inventions of claims 1 to 3, compounds represented by the formula (I) include ones having the effect of increasing retinoid actions and ones having the effect of suppressing retinoid actions, whereas compounds represented by the formula (II) are ones having the effect of suppressing retinoid actions. Since the effect of increasing retinoid actions and the effect of suppressing retinoid actions both as the technical feature are contradictory to each other, it is not considered that all of the alternative descriptions disclosed in each of claims 1 to 3 have a common nature or activity. Such being the case, these two inventions are not considered as relating to a group of inventions so linked as to form a single general

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/JP98/5091

Continuation of Box No. II of continuation of first sheet (1)

inventive concept.

## A. 発明の属する分野の分類 (国際特許分類 (IPC))

Int. Cl<sup>8</sup> C 07 D 277/34, 417/10,  
A 61 K 31/425, 31/55

## B. 調査を行った分野

## 調査を行った最小限資料 (国際特許分類 (IPC))

Int. Cl<sup>8</sup> C 07 D 277/34, 417/10,  
A 61 K 31/425, 31/55

最小限資料以外の資料で調査を行った分野に含まれるもの

## 国際調査で使用了電子データベース (データベースの名称、調査に使用した用語)

CAPLUS (STN), REGISTRY (STN), WPIDS (STN), MEDLINE (STN)

## C. 関連すると認められる文献

引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
A	WO, 97/11061, A1 (日研化学株式会社), 27. 3月. 1997 (27. 03. 97), & CA, 2233012, A, & NO, 9801269, A, & AU, 9670015, A1, & JP, 10-59951, A2	1-5
A	JP, 7-17854, A (ヘキストジャパン株式会社), 20. 1月. 1995 (20. 01. 95), & EP, 619116, A2, & CA, 2120424, AA, & US, 5525618, A, & US, 5716995, A,	1-5

☒ C欄の続きにも文献が列挙されている。

☐ パテントファミリーに関する別紙を参照。

## \* 引用文献のカテゴリー

「A」 特に関連のある文献ではなく、一般的技術水準を示すもの

「E」 国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの

「I」 優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献 (理由を付す)

「O」 口頭による開示、使用、展示等に言及する文献

「P」 国際出願日前で、かつ優先権の主張の基礎となる出願

の日の後に公表された文献

「T」 国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの

「X」 特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの

「Y」 特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの

「&」 同一パテントファミリー文献

国際調査を完了した日

18. 01. 99

国際調査報告の発送日 26.01.99

国際調査機関の名称及びあて先

日本国特許庁 (ISA/J P)

郵便番号100-8915

東京都千代田区霞が関三丁目4番3号

特許庁審査官 (権限のある職員)

瀬下 浩一 印

4 C

9736

電話番号 03-3581-1101 内線 3452

C (続き) . 関連すると認められる文献		
引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
P X P A	& US, 5703128, A, & US, 5767146, A EBISAWA, M., et al., 'NOVEL THIAZOLIDINEDIONE DERIVATIVES WI TH RETINOID SYNERGENIC ACTIVITY', Biol. Pharm. Bull., 21(5), May 1998, pp.547-549.	1 - 4 5

## 第 I 欄 請求の範囲の一部の調査ができないときの意見 (第 1 ページの 2 の続き)

法第 8 条第 3 項 (PCT 17 条(2)(a)) の規定により、この国際調査報告は次の理由により請求の範囲の一部について作成しなかった。

1. ☐ 請求の範囲 \_\_\_\_\_ は、この国際調査機関が調査をすることを要しない対象に係るものである。つまり、
2. ☐ 請求の範囲 \_\_\_\_\_ は、有意義な国際調査をすることができる程度まで所定の要件を満たしていない国際出願の部分に係るものである。つまり、
3. ☐ 請求の範囲 \_\_\_\_\_ は、従属請求の範囲であって PCT 規則 6.4(a) の第 2 文及び第 3 文の規定に従って記載されていない。

## 第 II 欄 発明の単一性が欠如しているときの意見 (第 1 ページの 3 の続き)

次に述べるようにこの国際出願に二以上の発明があるとこの国際調査機関は認めた。

請求の範囲 1 - 3 の発明について、式(I)で表される化合物は、レチノイドの作用を増強する作用を有するものと抑制する作用を有するものを包含し、また、式(II)で表される化合物はレチノイドの作用を抑制する作用を有するものであり、それらの技術的特徴であるレチノイドの作用を増強する作用及び抑制する作用は相反するものであるから、請求の範囲 1 - 3 において単一の請求の範囲に記載されたすべての択一的記載が共通の性質又は活性を有しているとは認められず、両者は単一の一般的発明概念を形成するように関連している発明に該当しない。

1. ☐ 出願人が必要な追加調査手数料をすべて期間内に納付したので、この国際調査報告は、すべての調査可能な請求の範囲について作成した。
2. ☒ 追加調査手数料を要求するまでもなく、すべての調査可能な請求の範囲について調査することができたので、追加調査手数料の納付を求めなかった。
3. ☐ 出願人が必要な追加調査手数料を一部のみしか期間内に納付しなかったため、この国際調査報告は、手数料の納付のあった次の請求の範囲のみについて作成した。
4. ☐ 出願人が必要な追加調査手数料を期間内に納付しなかったため、この国際調査報告は、請求の範囲の最初に記載されている発明に係る次の請求の範囲について作成した。

追加調査手数料の異議の申立てに関する注意

- ☐ 追加調査手数料の納付と共に出願人から異議申立てがあった。
- ☐ 追加調査手数料の納付と共に出願人から異議申立てがなかった。

### Specification

Retinoid receptor agonist.

### The Field of Technology

This invention relates to retinoid receptor active substance having the same physiological action as retinoid such as retinoic acid or the like, or an action to regulate the action of retinoid, and a drug including as an active ingredient the said compound.

### Background Technique

Retinoic acid (vitamin A acid) is an active metabolite of vitamin A, and has extremely important physiological effects such as action to cause differentiation of premature developing cells into mature cells having specific function, cell proliferation facilitation action, life maintenance action or the like. Vitamin A derivatives that have been synthesised so far, for example benzoic acid derivative in accordance with Kokai 61-22047 and Kokai 61-76440, compound in accordance with Journal of Medicinal Chemistry (988, Vol. 31, No. 11, p.2182) have been elucidated to have similar physiological effects. The aforesaid compounds having physiological activity of retinoic acid and retinoic acid-like action are known generally as "retinoid".

For example, all-trans retinoic acid binds as ligand to retinoic acid receptor (RAR) belonging to nuclear receptor superfamily (Evans, RM, Science, 240, p.889, 1988) present in cell nucleus, and is known to control the proliferation and differentiation of animal cells or cell death (Petkovich, M, et al., Nature, 330, pp.444-450, 1987). The aforesaid compound having retinoic acid-like physiological activity (for example, 4-[[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl] carbamoyl] benzoic acid: Am80 or the like) is suggested to bind to RAR in the same way as retinoic acid, too, and to display physiological activity (cf. Hashimoto, Y, Cell struct. Funct., 16, pp.113-123, 1991, Hashimoto, Y., et al., Biochem-Biophys. Res. Commun., 166, pp.1300-1307, 1990).

These compounds have been found to be clinically useful in prevention and treatment of vitamin A deficiency, keratosis of epithelial tissue, rheumatism, delayed type allergy, bone disease and leukemia and certain types of cancer. However, because these retinoids have various physiological activities, they cannot necessarily be regarded as satisfactory drugs from the viewpoint of side effects. Accordingly, creation of retinoid having characteristic action and the control molecule thereof are desired earnestly.

As action modifier of retinoid, benzodiazepine derivatives such as 4-[5H-2,3-(2,5-dimethyl-2,5-hexano)-5-methyldibenzo[b,e][1,4]diazepin-11-yl] benzoic acid and 4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]-benzoic acid or the like are known (PCT/JP96/2709, international disclosure WO97/11061). These compounds do not have retinoid

action by itself or the retinoid action thereof is weak, nevertheless has an action to markedly reinforce the action of retinoid such as retinoic acid or the like, and are suggested to be useful in prevention and treatment of vitamin A deficiency, keratosis of an epithelial tissue, rheumatism, delayed allergy, bone disease or leukemia and certain types of cancer.

As for the expression of physiological activity of retinoic acid, the presence of retinoid X receptor (RXR, 9-cis-retinoic acid is the ligand) is shown. It has been elucidated that the retinoid X receptor forms a dimer with retinoic acid receptor (RAR), and controls expression of physiological activity of retinoic acid by inducing or inhibiting transcription of gene (Mangelsdorf, D.J. et al., Nature, 345, pp.224-229). It has also been elucidated that in addition to retinoic acid receptor (RAR), retinoid X receptor (RXR) binds to receptor of active vitamin D3 in the nucleus, and PPAR said to be involved in fat metabolism, and other receptor species and controls the expression of action of physiologically active substance such as vitamin D3 and thyroxine or the like that bind to these receptors (Mangelsdorf, D. J. et al., the Retinoids, 2nd Ed., Ravan Press, pp.319-350, 1994).

Moreover as retinoid action modifier, presence of the compounds that act antagonistically with respect to retinoid and causes attenuation of typical retinoid actions are also known (Eyrolles, L, et al., Journal of Medicinal Chemistry, 37(10), pp.1508-1517, 1994). For example, it is disclosed in this publication that compounds such as 4-(5H-7,8,9,10-tetrahydro-5,7,7,10,10-pentamethyl benzo[e]naphtho[2,3-b][1,4]diazepin-13-yl) benzoic acid or the like act as antagonist of retinoid. Moreover, compounds such as 4-(13H-10,11,12,13-tetrahydro-10,10,13,13,15-pentamethyl dinaphtho[2,3-b][1,2-e][1,4]diazepin-7-yl) benzoic acid or the like have been found as retinoid antagonist by these inventors (JPA-7-255912 specification).

On the other hand, in the prior art, the carboxyl group of retinoids such as retinoic acid and Am80 or the like or the carboxyl group of the aforesaid retinoid action potentiating compound and retinoid antagonist is considered to be an essential functional group in each desired physiological activity, and when it is substituted with functional group such as sulfonamide, tetrazole or the like, it is known to lose the desired physiological activity. Although compounds having thiazolidine skeleton such as diglitazone, troglitazone or the like are indicated to act on  $\gamma$  subtype of PPAR (peroxisome proliferator-activated receptor) belonging to nuclear receptor superfamily, but in the prior art, it is not at all known that the compounds in which the carboxyl group of the said physiologically active compound was replaced with thiazolidine ring interact with retinoid receptor and display physiological activity.

As thiazolidinedione derivative, N-benzyl type 2,4-thiazolidinedione derivative having blood sugar lowering action is known (Kokai 9-48771 and The 17th medicinal chemistry symposium, The 6th Drug Chemistry sectional meeting annual meeting proceeding collection, pp.114-115, 1-P-30,

October 27, 1997, Pharmaceutical Society of Japan Publication). However, there is no suggestion at all about these thiazolidinedione derivatives have retinoid-like action or function as retinoid action modifier.

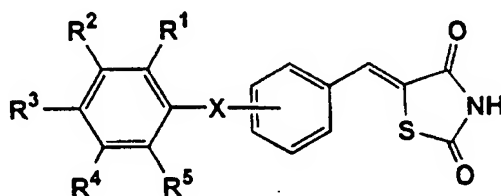
### Disclosure of the Invention

The object of this invention is to put forward retinoid receptor active substance having retinoid-like action or control action (for example, action to reinforce or inhibit the action of retinoid) with respect to action of retinoid. Another objection of this invention is to put forward a drug including as an active ingredient the aforesaid compound.

These inventors carried out assiduous investigations, and as a result, discovered that thiazolidine compounds represented by the following general formula had retinoic acid-like biological action, or had action to potentiate or inhibit the action of retinoid. This invention was completed on the basis of this discovery.

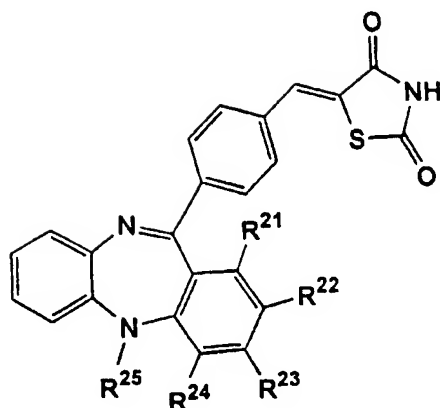
In other words, this invention puts forward:

A compound represented by the following general formula (I)



(wherein, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> each independently denote hydrogen atom or lower alkyl group, and among these, two adjacent groups may be linked together with carbon atoms on phenyl ring that they are bonded to form a 5-membered ring or 6-membered ring optionally having alkyl group of more than 1 or 2, X denotes a group represented by -C(R<sup>6</sup>)=CH-, -CH=C(R<sup>7</sup>)-, -N(R<sup>8</sup>)-CO-, -CO-N(R<sup>9</sup>)-, -C(CH<sub>2</sub>R<sup>10</sup>), -CO- or -NR<sup>11</sup>- (wherein, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> and R<sup>11</sup> each independently denote hydrogen atom or lower alkyl group)), or

A compound represented by following general formula (II)



(wherein, R<sub>21</sub>, R<sub>22</sub>, R<sub>23</sub> and R<sub>24</sub> each independently denote hydrogen atom or lower alkyl group, and among these, two adjacent groups may be linked together with carbon atoms on phenyl ring that they are bonded to form a 5-membered ring or 6-membered ring optionally having alkyl group of more than 1 or 2, and R<sub>25</sub> denotes a hydrogen atom or lower alkyl group).

From another viewpoint, a drug including as an active ingredient a compound represented by the aforesaid general formula, physiologically acceptable salts thereof and hydrates thereof and the solvate thereof is put forward. This drug is useful as retinoid-like agonist or retinoid action modifier (preferably retinoid action promoter or retinoid action depressant).

From another viewpoint, it is put forward the use of the aforesaid substances for the production of the said drug, and a process of a kind which is a preventive and/or therapeutic process of diseases involving nuclear receptor superfamily (Evans, R.M, Science, 240, p.889, 1988), preferably retinoid receptor (RAR and/or RXR), including a step to administer an effective quantity of the aforesaid substance to mammals including humans.

#### Ideal form for Carrying Out the Invention

In the aforesaid general formula (I), R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> each independently denote hydrogen atom or lower alkyl group. As lower alkyl group, it is possible to use carbon number 1-6 approx and preferably carbon number 1-4 straight chain or branched chain alkyl group. For example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, sec-butyl group or tert-butyl group or the like can be used.

Moreover, two adjacent groups selected from R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> may be linked together with carbon atoms on phenyl ring that they are bonded to form one or two, preferably one 5-membered ring or 6-membered ring optionally having alkyl group of more than 1 or 2. As the alkyl group which can be substituted on ring, it is possible to use carbon number 1-6 approx and preferably carbon number 1-4 straight chain or branched chain alkyl group. For example, methyl group, ethyl

group or the like can be used, and it is preferably substituted with 2-4 methyl groups, more preferably 4 methyl groups. For example, 5,6,7,8-tetrahydronaphthalene ring and 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene ring or the like may preferably be formed by R2 and R3 with phenyl ring that R2 and R3 substitute.

X denotes an any group represented by -C(R6)=CH-, -CH=C(R7)-, -N(R8)-CO-, -CO-N(R9)-, -C(CHR10), -CO- or -NR11-. In these groups, R6, R7, R8, R9, R10 and R11 each independently denote hydrogen atom or lower alkyl group, and as lower alkyl group, it is possible to use straight chain or branched chain alkyl group of carbon number 1-4. In a further embodiment, preferably methyl group, ethyl group or the like is used. The site of substitution of X is not restricted in particular on phenyl group of benzylidene thiazolidinedione moiety, however, it is preferably meta-substituted or para-substituted.

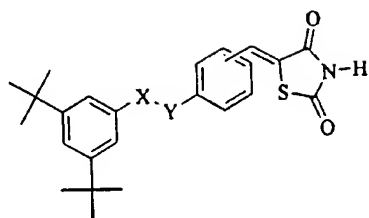
In the aforesaid general formula (II), R21, R22, R23 and R24 each independently denote hydrogen atom or lower alkyl group. As lower alkyl group, it is possible to use carbon number 1-6 approx and preferably carbon number 1-4 of straight chain or branched chain alkyl group. For example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, sec-butyl group or tert-butyl group or the like can be used. R25 denotes a hydrogen atom or lower alkyl group, but as lower alkyl group, it is possible to use straight chain or branched chain alkyl group of carbon number 1-4. In a further embodiment, preferably methyl group, ethyl group or the like can be used.

Moreover, two adjacent groups selected from R21, R22, R23 and R24 may be linked together with carbon atoms on phenyl ring that they are bonded to form one or two, preferably one 5-membered ring or 6-membered ring optionally having alkyl group of more than 1 or 2. As the alkyl group which can be substituted on ring, it is possible to use carbon number 1-6 approx and preferably carbon number 1-4 straight chain or branched chain alkyl group. For example, methyl group, ethyl group or the like can be used, and it is preferably substituted with 2-4 methyl groups, more preferably 4 methyl groups. For example, by R22 and R23 with phenyl ring that R22 and R23 substitute, it is preferred 5,6,7,8-tetrahydronaphthalene ring and 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene ring or the like to be formed.

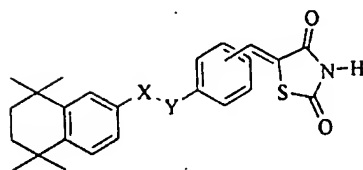
As for the aforesaid compound, base addition salt may be formed, and such salt may present as for example metal salt such as sodium salt, potassium salt, magnesium salt, calcium salt or the like, ammonium salt or organic amine salt or the like such as ethanolamine salt, triethylamine salt or the like. However, the physiologically acceptable salts among such salts can be used as effective ingredient of drug of this invention. Moreover, as for the aforesaid compound, there may be contained 1 or 2 or more asymmetric carbons corresponding to the kind of substituents, and in such case, arbitrary optical isomers on the basis of these asymmetric carbons, arbitrary mixture of optical

isomers, racemic body, diastereoisomer on the basis of asymmetric carbons of two or more, arbitrary mixture of diastereoisomers or the like can be included. Moreover, geometric isomer on the basis of cis- or trans-bond of double bond and arbitrary mixture of geometric isomer, and arbitrary hydrate or solvate of free compound or compound of a salt form, can also be included.

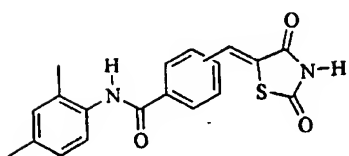
Among the compounds of this invention, the following compounds are nominated as preferred compounds, however, the compounds of this invention or the compounds which can be used as effective ingredient of drug of this invention needs not to be restricted to following compound (in the following explanation, para and meta respectively denotes that the site of substitution of X is para position and meta position on phenyl group of benzylidene thiazolidinedione moiety, and Me denotes methyl group).



	X	Y	thiazolidine
TZ151	C=O	NH	para
TZ153	C=O	NH	meta
TZ155	NH	C=O	para
TZ157	NH	C=O	meta
TZ161	C=O	NMe	para
TZ163	C=O	NMe	meta
TZ165	NMe	C=O	para
TZ167	NMe	C=O	meta

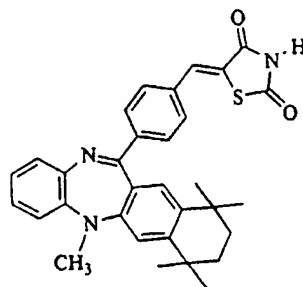


	X	Y	thiazolidine
TZ181	C=O	NH	para
TZ183	C=O	NH	meta
TZ185	NH	C=O	para
TZ187	NH	C=O	meta
TZ191	C=O	NMe	para
TZ193	C=O	NMe	meta
TZ195	NMe	C=O	para
TZ197	NMe	C=O	meta

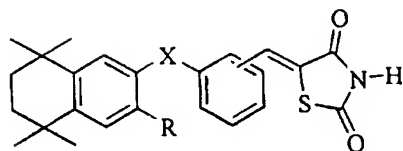


TZ175  
TZ177

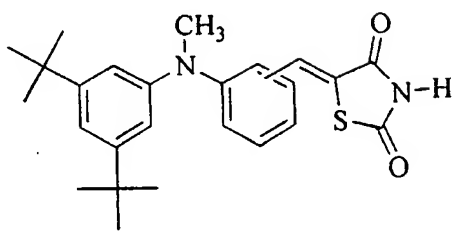
thiazolidine  
para  
meta



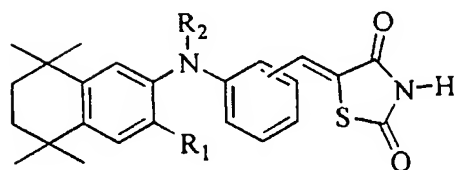
TZ201



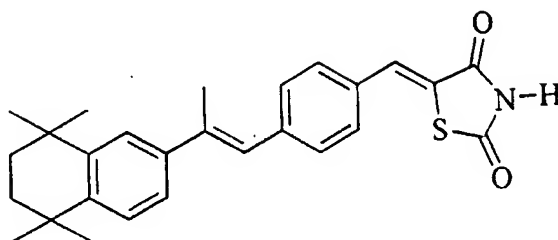
	X	R	thiazolidine
TZ221	C=O	H	para
TZ223	C=O	H	meta
TZ225	C=O	Me	para
TZ227	C=O	Me	meta
TZ241	C=C	H	para
TZ243	C=C	H	meta
TZ245	C=C	Me	para
TZ247	C=C	Me	meta



thiazolidine  
TZ315 para  
TZ317 meta



	R <sub>1</sub>	R <sub>2</sub>	thiazolidine
TZ321	H	H	para
TZ323	H	H	meta
TZ325	H	Me	para
TZ327	H	Me	meta
TZ331	Me	H	para
TZ333	Me	H	meta
TZ335	Me	Me	para
TZ337	Me	Me	meta



**TZ91**

As for the process for the production of compounds of aforesaid formula (I) and formula (II), Synthesis Examples of the aforesaid representative compounds are described in details in the Examples of this specification. Accordingly, arbitrary compounds included by the compounds of this invention represented by aforesaid general formula (I) or (II) can be easily produced by a person skilled in the art by referring to these Examples or in accordance with requirements by adding suitable alteration or modification to these processes.

Compound of the aforesaid formula (I) and formula (II) can interact with respect to retinoid receptor (the term of "retinoid receptor" used in this specification includes retinoic acid receptor RAR and RXR, and refers to one or two or more receptors with which retinoids such as retinoic

acid or the like can interact), and it either displays retinoid-like physiological activity by itself as agonist or has an action to enhance or inhibit the physiological activity of retinoid.

Accordingly, the drug including as an active ingredient the aforesaid compound is useful as retinoid-like agonist or retinoid action modifier. Which of the aforesaid action is displayed by the compound of the aforesaid formula (I) and formula (II) can be easily confirmed by the process described in detail in Examples of this specification. Moreover, there is a description in international disclosure WO97/11061 (PCT/JP96/2709) about evaluation process of retinoid action potentiating compound, and there is description in Eyrolles, L., et al., Journal of Medicinal Chemistry, 37(10), pp.1508-1517, 1994 and JPA-7-255912 specification about the evaluation process of retinoid action inhibitory compound.

Among the aforesaid compounds, the compounds having retinoid-like action have for example cell differentiation action, cell proliferation facilitation action, and life maintenance action or the like, and it can be used as effective ingredient of drug for prevention / therapy of vitamin A deficiency, keratosis of an epithelial tissue, psoriasis, allergic disease, immunologic disease such as rheumatism or the like, bone disease, leukemia or cancer.

Moreover, among the aforesaid compounds, the retinoid action potentiating compounds do not substantially have retinoid-like action, or have weak to moderate retinoid-like action, nevertheless, when the said compounds are placed in the co-presence of retinoid such as retinoic acid or the like, the physiological activity of retinoid (as typical examples, cell differentiation action, cell proliferation facilitation action, and life maintenance action or the like) is markedly enhanced.

No specific theory is adhered to, but when such retinoid action potentiating compound itself contains retinoid-like action, then the action thereof is synergistic action. Accordingly, when retinoids including retinoic acid or the aforesaid compound having retinoic acid-like biological action (for example, 4-[[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl] carbamoyl] benzoic acid: Am80) is administered as a drug for prevention or therapy of vitamin A deficiency, keratosis of epithelial tissue, psoriasis, allergic disease, immunologic disease such as rheumatism or the like, bone disease, leukemia or cancer, retinoid action potentiating compound can be used as action promoter of said retinoid.

Moreover, the aforesaid retinoid action potentiating compound enhances the action of retinoic acid present in the body even when retinoid is not administered for prevention or therapy of the said diseases, therefore, the aforesaid compound can be administered as a drug for the purpose of prevention or therapy of the said diseases. Furthermore, not only can these compounds have action potentiation with respect to retinoid, but also be used as action enhancer of physiologically active

substances such as steroidal compound, vitamin D compound such as vitamin D3 or the like or thyroxine or the like, which display physiological effect by binding to receptors belonging to nuclear receptor superfamily (Evans, RM, Science, 240, p.889, 1988) which is present in the nucleus of the cell. For example, it is useful as drug for prevention and/or therapy of diseases such as diabetes mellitus, arteriosclerosis, hyperlipidemia, hypercholesterolemia, bone disease, rheumatism or immunologic disease or the like.

As such nuclear receptors, for example, nuclear receptor of active vitamin D3, PPAR participating in fat metabolism, thyroxine receptor, and COUP or the like are known (as for the aforesaid receptors, cf. Mangelsdorf, D.J. et al., the Retinoids, 2nd Ed., Ravan Press, pp.319-350, 1994), it has been elucidated that these receptors in each case display the action of the said physiologically active substances by binding to retinoid X receptor (RXR).

Among the aforesaid compounds, retinoid action inhibitory compounds have action to markedly inhibit physiological action of retinoid (as typical examples, cell differentiation action, cell proliferation facilitation action, and life maintenance action or the like). No specific theory is adhered to, but it is considered that the compounds having such action bind to retinoid X receptor (RXR) that forms a dimer with retinoic acid receptor (RAR), and control the expression of physiological activity of retinoid such as retinoic acid or the like. These compounds are useful for prevention and/or therapy of endogenous vitamin A excess due to excess vitamin A in body, or exogenous vitamin A excess induced by retinoic acid or compound having retinoic acid-like biological action (for example, 4-[[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl] carbamoyl] benzoic acid: Am80) to be administered for prevention or therapy of vitamin A deficiency, keratosis of epithelial tissue, psoriasis, allergic disease, immunologic disease such as rheumatism or the like, bone disease, leukemia or cancer.

The retinoid action inhibitory compound can be administered by itself or in combination with other retinoid and anti-cancer agent, thereby cancer such as leukemia or the like can be treated. Moreover, the aforesaid compounds can suppress the action of substances, which display physiological effect by binding to receptors belonging to nuclear receptor superfamily (Evans, RM, Science, 240, p.889, 1988) which is present in the nucleus of the cell, such as steroidal compound, vitamin D compound such as vitamin D3 or the like or thyroxine or orphan receptor with unknown ligand or the like, therefore can be used for controlling the expression of the physiological action of these substances. Accordingly, the retinoid action inhibitory compound that binds to retinoid X receptor (RXR) can be used for prevention and/or therapy of diseases accompanied by aberration of biological action involving 1 or 2 or more of nuclear receptors belonging to nuclear receptor superfamily.

Drug of this invention contains as an active ingredient at least one of substance selected from the group comprising compound represented by the aforesaid formula (I), salts thereof, and hydrates thereof and solvate, or substance selected from the group comprising compound represented by the aforesaid formula (II), salts thereof and hydrates thereof and solvate. As drug of this invention, the aforesaid substance may be administered by itself, but preferably, it can be administered as medicinal composition of oral use or parenteral use that can be produced by process well-known to a person skilled in the art. As composition for drug suited for oral administration, for example, tablet, encapsulated formulation, powder, fine granules, granule, liquid agent and syrup or the like may be proposed, and for example injection, suppository, inhalant, instillation, collunarium, ointment, cream agent, and patch or the like are nominated as the medicinal composition suitable for parenteral administration.

The aforesaid medicinal composition can be produced by addition of pharmacologically and pharmaceutically permitted additives. For example, as examples of pharmacologically and pharmaceutically permitted additives, excipient, disintegrating agent or disintegration adjuvant, binding agent, lubricant, coating agent, dye, diluent, base, solvent or solubilizer, isotonicizing agent, pH modifier, stabilising agent, propellant, and binder or the like may be proposed.

Dose of drug of this invention is not restricted in particular, and it can be suitably selected corresponding to kind of action thereof or the strength and weakness or the like for a product, and also it is possible to suitably increase and decrease corresponding to various kinds of factors to be considered such as body weight, age of the patient, type of diseases, symptoms, administration route or the like. Generally, for the drug containing as an active ingredient compound having retinoid-like action, the dose thereof is referred to in accordance with the dose used for retinoic acid or the like as drug, and it can be suitably selected. For example, in case of oral administration, it is possible to be used with range of about 0.01-1,000mg per day per adult. Moreover, the dose can be selected in the same way about the drug including as an active ingredient retinoid action potentiating or retinoid action inhibitory compound, and it can be used per day per adult with range of about 0.01-1,000mg in the case of oral administration.

### **Examples**

Hereinafter, this invention will be described in greater detail using Examples. However, the range of the invention needs not to be restricted to the range of the following Examples. Moreover, the compound number in Examples corresponds to the number shown as preferred examples as above and the following synthesis scheme.

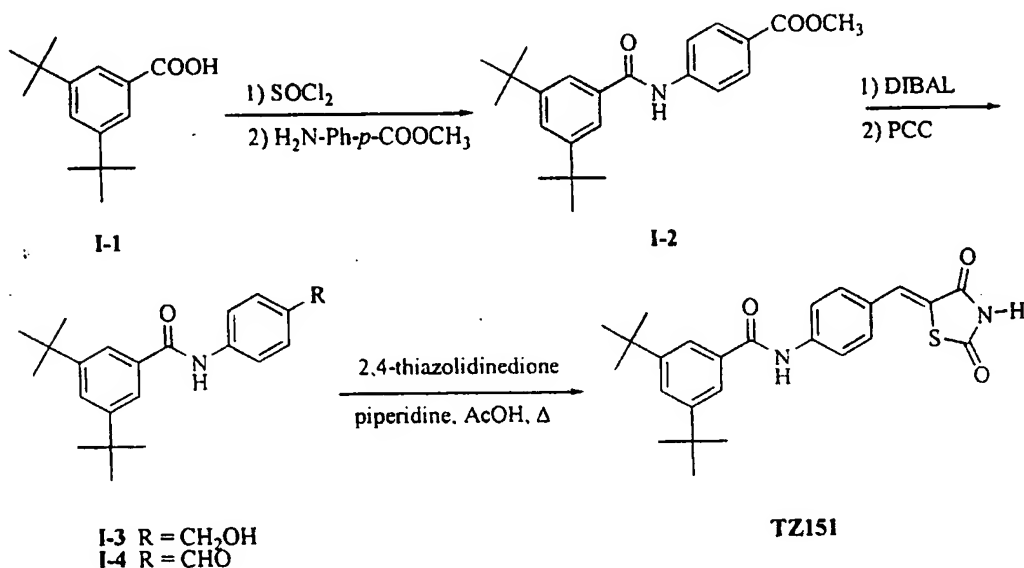
#### **Example 1: Synthesis of TZ91.**

4-[2-(5,6,7,8-tetramethyl-5,5,8,8-tetrahydro-2-naphthyl) propenyl] benzaldehyde 24 mg (0.072 mmol), 2,4-thiazolidinedione 10 mg (0.085 mmol) and piperidine 5 mg (0.058 mmol) were dissolved in ethanol 2.5 ml, and it was refluxed overnight. The reaction liquid was poured into 1N hydrochloric acid and extraction was carried out with ethyl acetate. The organic layer was washed with water, and it was dewatered with  $\text{Na}_2\text{SO}_4$ , and after the elimination of the solvent, it was recrystallised from methanol, and TZ91 (quantitative) was obtained.

TZ91: Yellow needles (methanol), mp 227-229°C;  $^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ) 8.24 (br s, 1H), 7.87 (s, 1H), 7.51 (d, 2H,  $J = 8.8$  Hz), 7.48 (d, 2H,  $J = 8.8$  Hz), 7.45 (d, 1H,  $J = 1.5$  Hz), 7.33 (d, 1H,  $J = 8.4$  Hz), 7.30 (dd, 1H,  $J = 8.4, 1.8$  Hz), 6.78 (br s, 1H), 2.32 (d, 3H,  $J = 1.5$  Hz), 1.71 (s, 4H), 1.34 (s, 6H), 1.31 (s, 6H),

Anal. Calcd. for  $\text{C}_{27}\text{H}_{29}\text{NO}_2\text{S}$ , C= 75.15%, H= 6.77%, N, 3.25%,  
Found C= 75.08%, H= 6.97 %, N, 3.11%.

**Example 2: Synthesis of TZ151.**



3,5-di-tert-butyl benzoic acid (I-1) 1.00 g (4.27 mmol) was suspended in thionyl chloride 2.50 g (21.0 mmol), anhydrous benzene 12 ml, and the suspension was refluxed for 14 hours. The thionyl chloride was eliminated by distillation, and p-aminobenzoic acid methyl ester 645mg (4.27 mmol) was added, and it was suspended in anhydrous benzene 30 ml, anhydrous pyridine 1 ml, and the mixture was stirred at room temperature for one hour 30 minutes. Iced water, 2N hydrochloric acid were added to the reaction liquid and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with  $\text{MgSO}_4$ , and it was

concentrated. It was purified by silica gel column chromatography (methylene chloride) and Compound I-2 was obtained 1.03 g (66 %).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 8.06 (d, 2H, J = 8.8 Hz), 7.90 (br s, 1H), 7.75 (d, 2H, J = 8.8 Hz), 7.66 (d, 2H, J = 1.5 Hz), 7.64 (t, 1H, J = 1.8 Hz), 3.92 (s, 3H), 1.37 (s, 18H).

Compound I-2, 1.02 g (2.78 mmol) was dissolved in THF 30 mL, and DIBAL 8.34 mL (1M toluene solution, 8.34 mmol) was gradually added at -20°C. 30 minutes later, the reaction liquid was discharged into 2N hydrochloric acid and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and thereafter the solvent was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 1) and Compound I-3 was obtained 786 mg (83 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 7.78 (br s, 1H), 7.67 (d, 2H, J = 1.8 Hz), 7.65 (d, 2H, J = 8.8 Hz), 7.62 (t, 1H, J = 1.8 Hz), 7.38 (d, 2H, J = 8.8 Hz), 4.69 (d, 2H, J = 5.9 Hz), 1.37 (s, 18H).

Compound I-3, 780 mg (2.30 mmol) was dissolved in methanol-free methylene chloride 22 ml, and PCC 992mg (4.60 mmol) was added and the mixture was stirred at room temperature for two hours 30 minutes. The reaction liquid was concentrated, and it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 4) and Compound I-4 was obtained 704 mg (91 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 9.96 (s, 1H), 7.97 (brs, 1H), 7.92 (d, 2H, J = 8.4 Hz), 7.85 (d, 2H, J = 8.4 Hz), 7.67 (d, 2H, J = 1.8 Hz), 7.66 (t, 1H, J = 1.8 Hz), 1.38 (s, 18H).

Compound I-4, 150mg (0.45 mmol), 2,4-thiazolidinedione 52 mg (0.45 mmol) were suspended in anhydrous toluene 10 ml, and a solution comprising piperidine 11 mg (0.13 mmol) and acetic acid 8 mg (0.13 mmol) dissolved in anhydrous toluene 1.4 ml was added, and the mixture was refluxed at 120°C for three hours 30 minutes. The reaction liquid was discharged into iced water and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and it was dewatered at MgSO<sub>4</sub>, and thereafter the solvent was concentrated, and TZ151 was obtained 194 mg (99 %).

TZ151: Yellow powder (ethyl acetate / n-hexane); mp >300°C, <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 10.43 (s, 1H), 7.93 (d, 2H, J = 8.4 Hz), 7.75 (s, 1H), 7.74 (d, 2H, J = 1.8 Hz), 7.63 (m, 3H), 1.35 (s, 18H),

Anal. Calcd. for C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>S, C= 68.78%, H= 6.46%, N= 6.42%,

Found C= 68.70%, H= 6.59%, N = 6.15 %.

#### Example 3: Synthesis of TZ153.

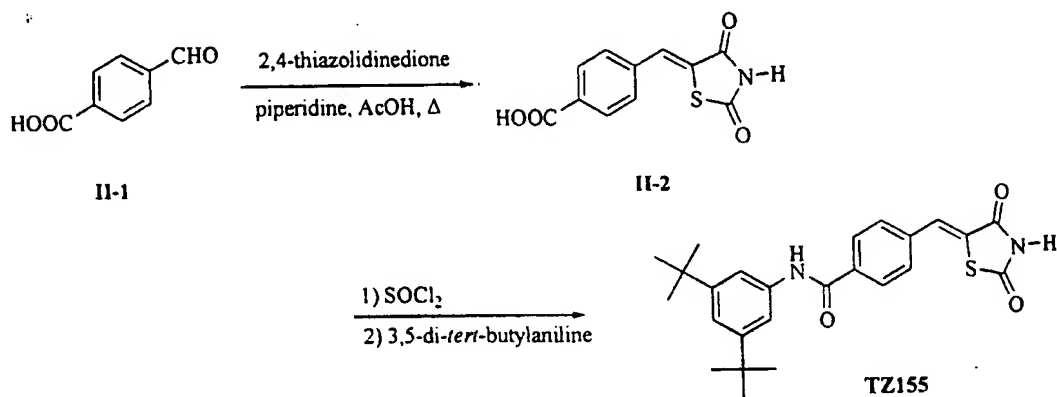
3,5-di-tert-butyl benzoic acid (I-1) and m-aminobenzoic acid methyl ester were used as the starting materials, and TZ153 was synthesised according to the process of Example 2.

TZ153: Pale yellow powder (ethyl acetate / n-hexane); mp 252°C, <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 10.36 (s, 1H), 8.16 (brs, 1H), 7.76 (m, 4H), 7.63 (t, 1H, J = 1.8 Hz), 7.52 (t, 1H, J = 8.1 Hz), 7.37 (d, 1H, J = 8.0 Hz), 1.35 (s, 18H);

Anal. Calcd. for C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>S, C= 68.78%, H= 6.46%, N= 6.42%,

Found C= 68.81%, H= 6.60%, N= 6.59 %.

**Example 4: Synthesis of TZ155.**



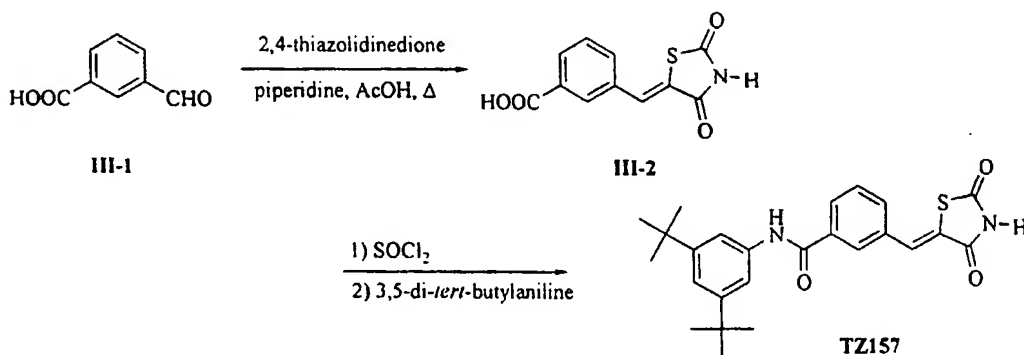
p-formyl benzoic acid (II-1) 1.00 g (6.67 mmol), 2,4-thiazolidinedione 858 mg (7.33 mmol) were suspended in anhydrous toluene 40 ml. The solution of piperidine 170 mg (2.00 mmol), acetic acid 120 mg (2.00 mmol) dissolved in anhydrous toluene 20 ml was added, and the mixture was refluxed at 120°C for six hours. The reaction liquid was cooled to room temperature, and the precipitated crystals were recovered by filtration and were washed with toluene, benzene, and 20 % acetone aqueous solution, and then dried, and Compound II-2 was obtained 1.57 g (94 %).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 8.04 (d, 2H, J = 8.4 Hz), 7.79 (s, 1H), 7.70 (d, 2H, J = 8.4 Hz).

Compound II-2, 250mg (1.00 mmol) was suspended in anhydrous benzene 12 ml, and SOCl<sub>2</sub> 627mg (5.27 mmol) was added, and the mixture was refluxed for 14 hours. SOCl<sub>2</sub> was eliminated by distillation, and thereafter, it was suspended in anhydrous benzene 10 ml, and 3,5-di-tert-butyl aniline 210 mg (1.00 mmol), anhydrous pyridine 4 ml were added, and the mixture was stirred at room temperature for two hours. 2N hydrochloric acid with floating ice was added to the reaction liquid and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 3 : 2) and TZ155 was obtained 390 mg (89 %).

TZ155: Pale yellow powder (ethyl acetate / n-hexane); mp 266-267°C, <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 10.20 (s, 1H), 8.08 (d, 2H, J = 8.4 Hz), 7.87 (s, 1H), 7.74 (d, 2H, J = 8.4 Hz), 7.69 (d, 1H, J = 1.5 Hz), 7.16 (t, 1H, J = 1.5 Hz), 1.30 (s, 18H),  
Anal. Calcd. for C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>S, C= 68.78%, H= 6.46%, N= 6.42%,  
Found C= 68.52%, H= 6.52%, N= 6.37%.

**Example 5: Synthesis of TZ157.**



m-formyl benzoic acid (III-1) 800 mg (5.33 mmol), 2,4-thiazolidinedione 686 mg (5.87 mmol) were suspended in anhydrous toluene 40 ml. Solution comprising piperidine 136 mg (1.60 mmol), acetic acid 96 mg (1.60 mmol) dissolved in anhydrous toluene 16 ml was added, and the mixture was refluxed at 120°C for four hours 30 minutes. The reaction liquid was cooled to room temperature, and the precipitated crystals were recovered by filtration and were washed with toluene, benzene, and 20 % acetone aqueous solution. and then dried, and Compound III-2 was obtained 1.017 g (77 %).

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 8.14 (s, 1H), 8.01 (d, 1H, J = 7.7 Hz), 7.86 (s, 1H), 7.85 (d, 1H, J = 7.7 Hz), 7.66 (t, 1H, J = 7.7 Hz).

Compound III-2, 250mg (1.00 mmol) was suspended in anhydrous benzene 14 ml, and SOCl<sub>2</sub> 627mg (5.27 mmol) was added, and the mixture was refluxed for 14 hours. SOCl<sub>2</sub> was eliminated by distillation, and thereafter, it was suspended in anhydrous benzene 10 ml, and 3,5-di-tert-butyl aniline 210 mg (1.00 mmol), anhydrous pyridine 4 ml were added, and the mixture was stirred at room temperature for two hours. 2N hydrochloric acid that ice was floated on was added to the reaction liquid and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 3 : 4) and TZ157 was obtained 292 mg (67 %).

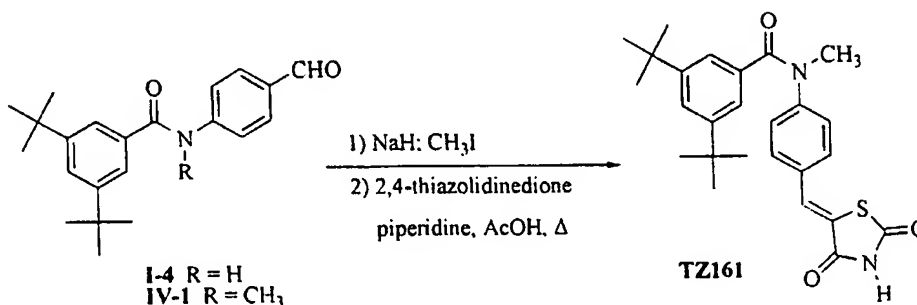
TZ157: Colorless needles (ethyl acetate / n-hexane); mp 263°C

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 10.20 (s, 1H), 8.15 (s, 1H), 8.04 (d, 1H, J = 7.7 Hz), 7.87 (s, 1H), 7.78 (d, 1H, J = 7.7 Hz), 7.69 (t, 1H, J = 7.7 Hz), 7.67 (d, 2H, J = 1.5 Hz), 7.17 (t, 1H, J = 1.5 Hz), 1.30 (s, 18H),

Anal. Calcd. for C<sub>25</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub>S, C = 68.78%, H = 6.46%, N = 6.42%,

Found C = 68.82%, H = 6.65%, N = 6.56 %.

**Example 6: Synthesis of TZ161.**



NaH 97.6mg (60 %, 2.45 mmol) was washed with n-hexane, and it was suspended in DMF 1 ml. Aldehyde I-4 (cf. Example 2) 550 mg (1.63 mmol) dissolved in DMF 10 ml was added, and the mixture was stirred at room temperature for 20 minutes. Methyl iodide 0.19 ml (3.05 mmol) was added, and the mixture was stirred for 45 minutes. The DMF was eliminated by distillation, water was added and the mixture was extracted with methylene chloride. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and thereafter the solvent was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and Compound IV-1 was obtained 389 mg (68 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 9.90 (s, 1H), 7.73 (d, 2H, J = 8.4 Hz), 7.31 (t, 1H, J = 1.8 Hz), 7.31 (t, 1H, J = 1.8 Hz), 7.15 (d, 2H, J = 8.4 Hz), 7.13 (d, 2H, J = 1.8 Hz), 3.56 (s, 3H), 1.14 (s, 18H).

Compound IV-1, 385mg (1.10 mmol), 2,4-thiazolidinedione 128 mg (1.10 mmol) were suspended in anhydrous toluene 8 ml, and a solution of piperidine 26 mg (0.33 mmol) and acetic acid 20 mg (0.33 mmol) dissolved in anhydrous toluene 3 ml was added, and the mixture was refluxed at 120°C for one hour 30 minutes. The reaction liquid was discharged into iced water, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and thereafter the solvent was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 1) and TZ161 was obtained 417 mg (84.5 %).

TZ161: Yellow plate (ethyl acetate / n-hexane); mp 265°C

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 7.70 (s, 1H), 7.46 (d, 2H, J = 8.4 Hz), 7.29 (t, 1H, J = 1.5 Hz), 7.26 (d, 2H, J = 8.4 Hz), 7.09 (d, 2H, J = 1.5 Hz), 3.41 (s, 3H), 1.12 (s, 18H),

Anal. Calcd. for C<sub>26</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>S, C= 69.31%, H= 6.71%, N= 6.22%,

Found C= 69.01%, H= 6.68%, N = 5.93 %.

**Example 7:** Synthesis of TZ163.

3-(3,5-di-tert-butylphenyl carbamoyl) benzaldehyde (synthesised in the same way as in Compound 1-4 from m-amino benzoic acid methyl ester) was used as starting material. TZ163 was synthesised according to the process of Example 6.

TZ163: Yellow plates (ethyl acetate / n-hexane); mp 195°C, <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 7.61 (s, 1H), 7.46 (t, 1H, J = 7.7 Hz), 7.38 (m, 2H), 7.27 (t, 1H, J = 1.8 Hz), 7.14 (brs, 1H), 7.08 (d, 2H, J = 1.8 Hz), 3.42 (s, 3H), 1.11 (s, 18H),

Anal. calcd. For C<sub>26</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>S, C= 69.31%, H= 6.71%, N= 6.22%,

Found C= 69.41%, H= 6.92%, N = 5.99 %.

**Example 8:** Synthesis of TZ165.

Thiazolidine II-2 (cf. Example 4) and 3,5-di-tert-butyl-N-methylaniline were used as starting materials. TZ165 was synthesised according to the process of Example 4 (79 %).

TZ165: Pale yellow prisms (ethyl acetate / n-hexane); mp 253-254°C, <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 7.67 (s, 1H), 7.38 (d, 2H, J = 8.4 Hz), 7.29 (d, 2H, J = 8.4 Hz), 7.11 (s, 1H), 6.93 (s, 2H), 3.42 (s, 3H), 1.12 (s, 18H),

Anal. Calcd. for C<sub>26</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>S, C= 69.31%, H= 6.71%, N= 6.22%,

Found C= 69.05%, H= 6.53%, N = 6.48 %.

**Example 9:** Synthesis of TZ167.

Thiazolidine III-2 (cf. Example 5) and 3,5-di-tert-butyl-N-methylaniline were used as starting materials. TZ167 was synthesised according to the process of Example 5 (76 %).

TZ167: Colorless prisms (ethyl acetate / n-hexane); mp 238°C

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 7.58 (s, 1H), 7.48 (m, 2H), 7.23 (brs, 1H), 7.10 (s, 1H), 6.93 (d, 2H, J = 1.5 Hz), 3.44 (s, 3H), 1.11 (s, 18H),

Anal. Calcd. for C<sub>26</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>S, C= 69.31%, H= 6.71%, N= 6.22%,

Found C= 69.13%, H= 6.78%, N = 6.34 %.

**Example 10:** Synthesis of TZ175.

2,4-xylylidine and thiazolidine II-2 (cf. Example 4) were used as starting materials. TZ175 was synthesised according to the process of Example 4 (88 %).

TZ175: Pale pink powder (methylene chloride / methanol); mp 269°C

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 9.89 (s, 1H), 8.08 (d, 2H, J = 8.4 Hz), 7.86 (s, 1H), 7.73 (d, 2H, J = 8.4 Hz), 7.21 (d, 1H, J = 8.1 Hz), 7.08 (s, 1H), 7.02 (d, 1H, J = 8.1 Hz), 2.29 (s, 3H), 2.20 (s, 3H),

Anal. Calcd. for C<sub>19</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>S, C= 64.76%, H= 4.58%, N= 7.95%,

Found C= 64.51%, H= 4.67%, N = 8.07 %.

**Example 11: Synthesis of TZ177.**

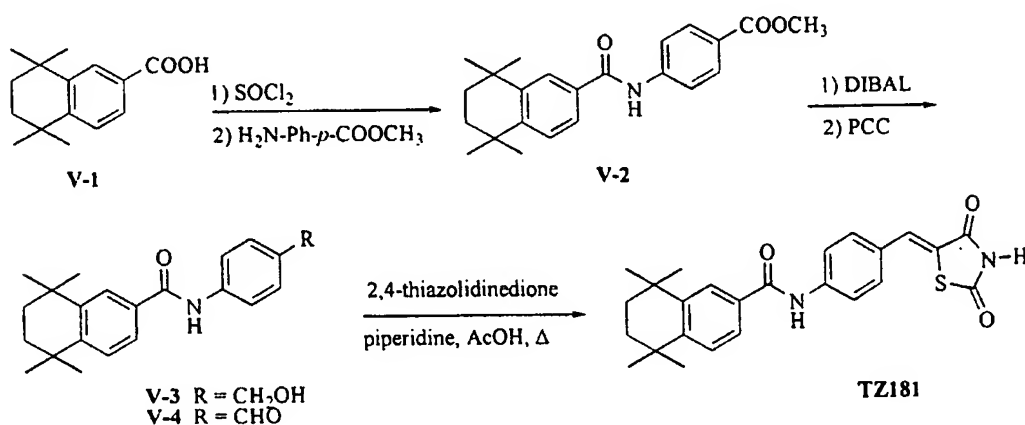
2,4-xylylidine and thiazolidine III-2 (cf. Example 5) were used as starting materials. TZ177 was synthesised according to the process of Example 5 (31 %).

TZ177: Colorless needles (methylene chloride / methanol); mp 245°C, <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 9.90 (s, 1H), 8.15 (s, 1H), 8.04 (d, 1H, J = 7.7 Hz), 7.87 (s, 1H), 7.79 (d, 1H, J = 8.1 Hz), 7.68 (t, 1H, J = 7.7 Hz), 7.23 (d, 1H, J = 8.1 Hz), 7.09 (s, 1H), 7.03 (d, 1H, J = 8.1 Hz), 2.29 (s, 3H), 2.21 (s, 3H),

Anal. Calcd. for C<sub>19</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>S, C= 64.76%, H= 4.58%, N= 7.95%,

Found C= 64.57%, H= 4.41%, N = 7.89 %.

**Example 12: Synthesis of TZ181.**



5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoic acid (V-1) 700 mg (3.01 mmol) was suspended in thionyl chloride 8 ml and 1 drop of DMF was added and the mixture was stirred at room temperature for two hours. The thionyl chloride was eliminated by distillation, and p-aminobenzoic

acid methyl ester 450mg (2.98 mmol) and 4-dimethylaminopyridine 5 mg were added, and it was dissolved in anhydrous pyridine 20 ml, and the mixture was stirred at room temperature overnight. The reaction liquid was poured into 2N hydrochloric acid, and extraction was carried out with ethyl acetate. The organic layer was washed with 2N hydrochloric acid, water, and aqueous sodium chloride, and it was dewatered with Na<sub>2</sub>SO<sub>4</sub>, and it was concentrated, and compound V-2 was obtained (97 %).

Compound V-2, 183mg (0.50 mmol) was dissolved in THF 10 mL, and DIBAL 1.5 mL (1M toluene solution, 1.5 mmol) was added at -45°C. 30 minutes later, the reaction liquid was discharged into 2N hydrochloric acid and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with Na<sub>2</sub>SO<sub>4</sub>, and thereafter the solvent was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : methylene chloride = 1 : 3) and compound V-3 was obtained 142 mg (84 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 7.86 (d, 1H, J = 2.2 Hz), 7.78 (brs, 1H), 7.63 (d, 2H, J = 8.4 Hz), 7.55 (dd, 1H, J = 2.0, 8.2 Hz), 7.40 (d, 1H, J = 8.8 Hz), 7.37 (d, 2H, J = 8.4 Hz), 4.68 (s, 2H), 1.72 (s, 4H), 1.33 (s, 6H), 1.31 (s, 6H).

Compound V-3, 140mg (0.42 mmol) was dissolved in methanol-free methylene chloride 10 ml, and PCC 100mg (0.46 mmol) was added and the mixture was stirred at room temperature for one hour. The reaction liquid was concentrated, and it was purified by silica gel column chromatography (methylene chloride) and compound V-4 was obtained 99 mg (71 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 9.95 (s, 1H), 7.92 (brs, 1H), 7.91 (d, 2H, J = 8.8 Hz), 7.87 (d, 1H, J = 1.8 Hz), 7.84 (d, 2H, J = 8.8 Hz), 7.56 (dd, 1H, J = 2.0, 8.3 Hz), 7.43 (d, 1H, J = 8.4 Hz), 1.73 (s, 4H), 1.34 (s, 6H), 1.32 (s, 6H).

Compound V-4, 73mg (0.22 mmol), 2,4-thiazolidinedione 30 mg (0.26 mmol) were suspended in anhydrous toluene 4 ml. Piperidine 173 µl and acetic acid 100 µl were dissolved in anhydrous toluene 25 ml, and solution 3 ml thereof were added, and it was refluxed at 120°C for two hours. The reaction liquid was discharged into iced water and extraction was carried out with ethyl acetate. The organic layer was washed with 2N hydrochloric acid, water, it was dewatered with Na<sub>2</sub>SO<sub>4</sub>, thereafter the solvent was concentrated, and TZ181 was obtained 100 mg (quantitative).

TZ181: Yellow needles (ethyl acetate / n-hexane); mp 288-290°C, <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 12.52 (s, 1H), 10.36 (s, 1H), 7.94 (d, 2H, J = 8.8 Hz), 7.88 (d, 1H, J = 2.2 Hz), 7.76 (s, 1H), 7.71 (dd, 2H, J = 2.2, 8.4 Hz), 7.60 (d, 2H, J = 8.8 Hz), 7.48 (d, 1H, J = 98.3 Hz), 1.68 (s, 4H), 1.31 (s, 6H), 1.28 (s, 6H),

Anal. Calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>S, C= 69.10%, H= 6.03%, N= 6.45%,  
Found C= 69.05%, H= 6.23%, N = 6.55 %.

**Example 13:** Synthesis of TZ183.

5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoic acid (V-1) and m-aminobenzoic acid methyl ester were used as starting materials. TZ183 was synthesised according to the process of Example 12.

TZ183: Colorless powder (ethyl acetate / n-hexane); mp 183°C, <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 10.29 (s, 1H), 8.15 (s, 1H), 7.88 (d, 1H, J = 1.8 Hz), 7.76 (d, 1H, J = 1.8 Hz), 7.26 (s, 1H), 7.26 (s, 1H), 6.71 (dd, 1H, J = 8.4Hz, 1.8 Hz), 6.50 (t, 1H, J = 7.7 Hz), 6.49 (d, 1H, J = 8.1 Hz), 6.35 (d, 1H, J = 2.1 Hz), 1.69 (s, 4H), 1.31 (s, 6H), 1.28 (s, 6H),  
Anal. Calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>S, C= 69.10%, H= 6.03%, N= 6.45%,  
Found C= 68.81%, H= 5.92%, N = 6.51 %.

**Example 14:** Synthesis of TZ185.

5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylamine and thiazolidine II-2 (cf. Example 4) were used as starting materials. TZ185 was synthesised according to the process of Example 4.

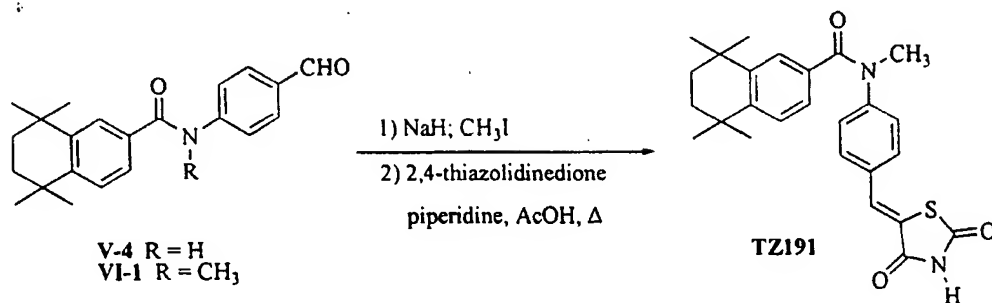
TZ185: Pale orange plates (ethyl acetate / n-hexane); mp 234°C, <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 10.18 (s, 1H), 8.07 (d, 2H, J = 8.4 Hz), 7.86 (s, 1H), 7.73 (d, 2H, J = 8.4 Hz), 7.68 (d, 1H, J = 2.2 Hz), 7.57 (dd, 1H, J = 8.4Hz, 2.2 Hz), 7.28 (d, 1H, J = 8.4 Hz), 1.65 (s, 4H), 1.25 (s, 6H), 1.24 (s, 6H),  
Anal. Calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>S, C= 69.10%, H= 6.03 %, N= 6.45  
Found C= 69.40%, H= 6.10%, N= 6.55%.

**Example 15:** Synthesis of TZ187.

5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylamine and thiazolidine III-2 (cf. Example 5) were used as starting materials. TZ187 was synthesised according to the process of Example 5.

TZ187: Colorless plates (ethyl acetate / n-hexane); mp 187°C, <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 10.18 (s, 1H), 8.14 (s, 1H), 8.03 (d, 2H, J = 7.7 Hz), 7.87 (s, 1H), 7.78 (d, 1H, J = 7.7 Hz), 7.68 (t, 1H, J = 7.7 Hz), 7.68 (d, 1H, J = 2.2 Hz), 7.56 (dd, 1H, J = 8.8Hz, 2.2 Hz), 7.29 (d, 1H, J = 8.4 Hz), 1.65 (s, 4H), 1.26 (s, 6H), 1.24 (s, 6H),  
Anal. Calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>S, C= 69.10%, H= 6.03%, N= 6.45%,  
Found C= 68.81%, H= 6.21%, N = 6.37 %.

Example 16: Synthesis of TZ191.



NaH 18mg (60 %, 0.45 mmol) was washed with n-hexane, and it was suspended in DMF 1 ml. Aldehyde V-4 (cf. Example 12) 100 mg (0.30 mmol) was dissolved in DMF 4 ml, and it was added and the mixture was stirred at room temperature for 15 minutes. Methyl iodide 0.07 ml (1.12 mmol) was added, and the mixture was stirred for 30 minutes. The DMF was eliminated by distillation, water was added and the mixture was extracted with methylene chloride. The organic layer was washed with aqueous sodium chloride, and was dehydrated with MgSO<sub>4</sub>, thereafter, the solvent were concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and compound VI-1 was obtained 388.9 mg (63 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 9.92 (s, 1H), 7.75 (d, 2H, J = 8.4 Hz), 7.24 (dd, 1H, J = 8.1, 1.8 Hz), 7.19 (d, 1H, J = 8.4 Hz), 7.18 (d, 1H, J = 8.4 Hz), 7.04 (d, 1H, J = 1.8 Hz), 3.55 (s, 3H), 1.60 (m, 4H), 1.20 (s, 6H), 0.93 (s, 6H).

Compound VI-1, 60 mg (0.17 mmol), 2,4-thiazolidinedione 20 mg (0.17 mmol) were suspended in anhydrous toluene 4 ml, and a solution of piperidine 4.4 mg (0.052 mmol) and acetic acid 3.1 mg (0.052 mmol) dissolved in anhydrous toluene 0.5 ml was added, and the mixture was refluxed at 120°C for 40 minutes. The reaction liquid was discharged into iced water, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and thereafter the solvent was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and TZ191 was obtained 417 mg (93 %).

TZ191: Yellow powder (ethyl acetate / n-hexane); mp 235°C, <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 7.71 (s, 1H), 7.48 (d, 2H, J = 8.8 Hz), 7.28 (d, 2H, J = 8.4 Hz), 7.27 (d, 1H, J = 8.4 Hz), 7.22 (dd, 1H, J = 8.4, 1.5 Hz), 6.98 (d, 1H, J = 1.8 Hz), 3.40 (s, 3H), 1.53 (m, 4H), 1.17 (s, 6H), 0.89 (s, 6H),

Anal. Calcd. for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>S, C= 69.62%, H= 6.29%, N= 6.24%,

Found C= 69.33%, H= 6.38%, N = 6.31%.

**Example 17:** Synthesis of TZ193.

3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl carbamoyl) benzaldehyde (synthesised in the same way as in compound V-4 from m-aminobenzoic acid methyl ester) was used as starting material. TZ193 was synthesised according to the process of Example 16.

TZ193: Colorless plates (ethyl acetate / n-hexane); mp 188°C, <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 7.64 (s, 1H), 7.47 (t, 1H, J = 7.7 Hz), 7.38 (m, 2H), 7.24 (d, 1H, J = 8.1 Hz), 7.16 (dd, 1H, J = 8.4, 1.8 Hz), 7.03 (d, 1H, J = 1.8 Hz), 3.41 (s, 3H), 1.52 (s, 4H), 1.14 (s, 6H), 0.91 (s, 6H),  
Anal. Calcd. for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>S, C= 69.62%, H= 6.29%, N= 6.24%,  
Found C= 69.65%, H= 6.16%, N= 6.08 %.

**Example 18:** Synthesis of TZ195.

It was synthesised (80 %) according to the process of Example 4 from thiazolidine II-2 (cf. Example 4) and 5,6,7,8-tetrahydro-N,5,5,8,8-pentamethyl-2-naphthylamine.

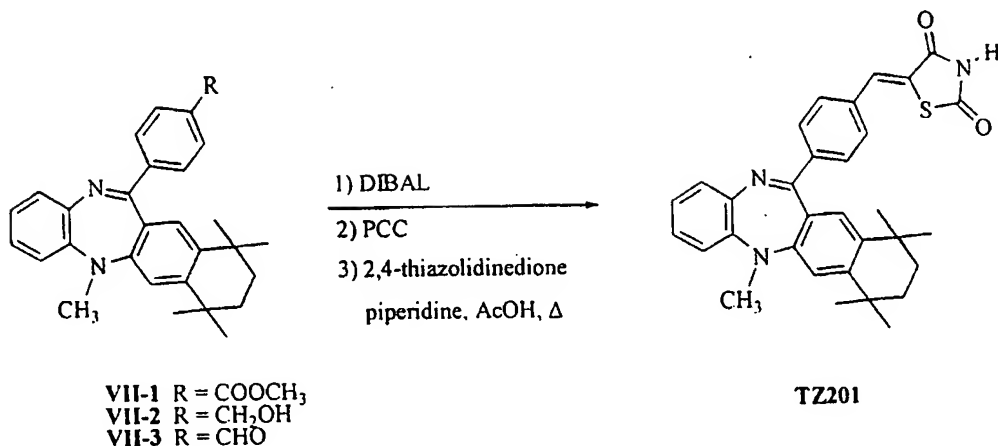
TZ195: Pale yellow plates (ethyl acetate / n-hexane); mp 233°C, <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 7.69 (s, 1H), 7.39 (d, 2H, J = 8.1 Hz), 7.31 (d, 2H, J = 8.1 Hz), 7.26 (d, 2H, J = 8.8 Hz), 7.06 (dd, 1H, J = 8.4, 2.6 Hz), 6.83 (brs, 1H), 3.37 (s, 3H), 1.50 (m, 4H), 1.16 (s, 6H), 0.91 (s, 6H),  
Anal. Calcd. for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>S, C= 69.62%, H= 6.29%, N= 6.24%,  
Found C= 69.38%, H= 6.42%, N= 6.02%.

**Example 19:** Synthesis of TZ197.

It was synthesised (70 %) according to the process of Example 5 from thiazolidine III-2 (cf. Example 5) and 5,6,7,8-tetrahydro-N,5,5,8,8-pentamethyl-2-naphthylamine.

TZ197: Pale yellow prisms (ethyl acetate / n-hexane); mp 237°C  
<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 7.59 (s, 1H), 7.48 (d, 1H, J = 7.0 Hz), 7.42 (m, 2H), 7.24 (d, 1H, J = 8.4 Hz), 7.19 (s, 1H), 7.04 (dd, 1H, J = 8.4, 2.2 Hz), 6.85 (d, 1H, J = 2.2 Hz), 3.41 (s, 3H), 1.51 (s, 4H), 1.14 (s, 6H), 0.91 (s, 6H),  
Anal. Calcd. for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>S, C= 69.62%, H= 6.29%, N= 6.24%,  
Found C= 69.51%, H= 6.37%, N= 6.27%.

**Example 20:** Synthesis of TZ201.



Ester body VII-1, 110mg (0.24 mmol) was dissolved in THF 10 mL, and DIBAL 1.5 mL (1M toluene solution, 1.5 mmol) was added at  $-20^{\circ}\text{C}$ . 3 hours later, the reaction liquid was discharged into 2N hydrochloric acid and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with Na<sub>2</sub>SO<sub>4</sub>, and thereafter the solvent was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : methylene chloride = 1 : 4) and compound VII-2 was obtained 100 mg (97 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 7.81 (d, 2H, J = 8.4 Hz), 7.40 (d, 2H, J = 8.4 Hz), 7.31 (d, 1H, J = 7.3 Hz), 7.13 (dt, 1H, J = 1-8, 7.3 Hz), 7.08 (dt, 1H, J = 1.5, 7.3 Hz), 6.97 (dd, 1H, J = 1.5, 7.7 Hz), 6.94 (s, 1H), 6.92 (s, 1H), 4.77 (d, 2H, J = 4.4 Hz), 3.25 (s, 3H), 1.64 (m, 4H), 1.32 (s, 3H), 1.26 (s, 3H), 1.14 (s, 3H), 1.05 (s, 3H).

Compound VII-2, 100mg (0.24 mmol) was dissolved in methanol-free methylene chloride 10 ml, and PCC 60mg (0.28 mmol) was added and the mixture was stirred at room temperature for one hour. The reaction liquid was concentrated, and it was purified by silica gel column chromatography (ethyl acetate : methylene chloride = 1 : 50) and compound VII-3 was obtained 72 mg (72 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 10.10 (2, 1H), 7.98 (d, 2H, J = 8.0Hz), 7.92 (d, 2H, J = 8.8 Hz), 7.32 (d, 1H, J = 7.7 Hz), 7.17 (dt, 1H, J = 1.5, 8.0 Hz), 7.10 (dt, 1H, J = 1.5, 7.7 Hz), 6.98 (dd, 1H, J = 1.5, 8.1 Hz), 6.93 (s, 1H), 6.86 (s, 1H), 3.26 (s, 3H), 1.65 (m, 4H), 1.32 (s, 3H), 1.27 (s, 3H), 1.12 (s, 3H), 1.04 (s, 3H).

Compound VII-3, 70mg (0.17 mmol), 2,4-thiazolidinedione 20 mg (0.17 mmol) were suspended in anhydrous toluene 4 ml. Piperidine 173 μl and acetic acid 100 μl were dissolved in anhydrous toluene 25 ml, and the solution 2.5 ml thereof was added, and it was refluxed at 120°C for two hours. The reaction liquid was discharged into iced water and extraction was carried out with ethyl

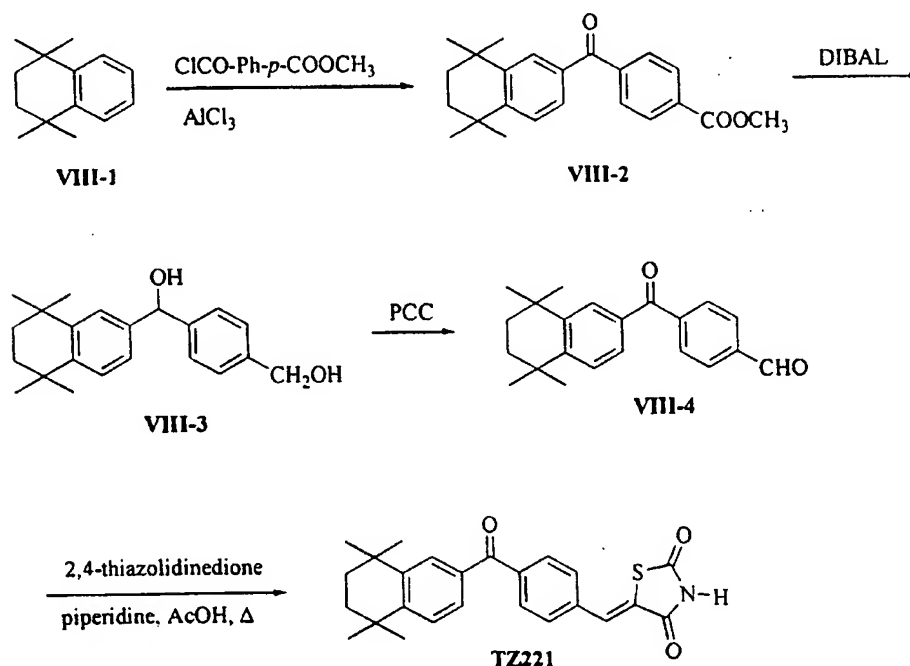
acetate. The organic layer was washed with 2N hydrochloric acid, water, and it was dewatered with  $\text{Na}_2\text{SO}_4$ , and thereafter the solvent was concentrated, and TZ201 was obtained 73 mg (84 %).

TZ201: Red needles (ethyl acetate / methanol); mp  $>300^\circ\text{C}$ ,  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ ,  $30^\circ\text{C}$ ) 12.62 (s, 1H), 7.83 (s, 1H), 7.82 (d, 2H,  $J = 8.7$  Hz), 7.69 (d, 2H,  $J = 8.3$  Hz), 7.16-7.22 (m, 2H), 7.09 (m, 2H), 7.06 (s, 1H), 6-90 (s, 1H), 3.21 (s, 3H), 1.62 (m, 4H), 1.30 (s, 3H), 1.26 (s, 3H), 1.13 (s, 3H), 1.03 (s, 3H),

Anal. Calcd. for  $\text{C}_{32}\text{H}_{31}\text{N}_3\text{O}_2\text{S}\cdot\text{H}_2\text{O}$ , C= 71.23%, H= 6.16%, N= 7.79%,

Found C= 71.12%, H= 6.02%, N= 7.71 %.

**Example 21:** Synthesis of TZ221.



1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (VIII-1) 1.00 g (5.32 mmol) and terephthalic acid monomethyl ester chloride 1.06 g (5.32 mmol) were dissolved in methanol-free methylene chloride 20 ml, and aluminum chloride 1.42 g (10.64 mmol) was added under ice cooling, and thereafter it was refluxed for 30 minutes. The reaction liquid was discharged into iced water and extraction was carried out with ethyl acetate. The organic layer was washed with water, aqueous sodium chloride, and it was dewatered with  $\text{MgSO}_4$  and thereafter, it was concentrated, thereafter, it was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 20 then 1 : 10), and thereby compound VIII-2 was obtained 1.3 g (70 %).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 8.14 (d, 2H, J = 8.4 Hz), 7.83 (d, 2H, J = 8.4 Hz), 7.78 (d, 1H, J = 1.8 Hz), 7.53 (dd, 1H, J = 8.4, 1.8 Hz), 7.40 (d, 1H, J = 8.0 Hz), 3.97 (s, 3H), 1.72 (s, 4H), 1.32 (s, 6H), 1.29 (s, 6H).

Compound VIII-2, 1.20 g (3.43 mmol) was dissolved in THF 15 mL under argon replacement, and DIBAL 13.7 mL (1M toluene solution, 13.7 mmol) was added dropwise while stirring at -78°C. One hour was allowed to pass, and the reaction liquid was discharged into 1N hydrochloric acid and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and after concentration, purification was carried out by silica gel column chromatography (ethyl acetate : hexane = 1 : 3) and as a result, because compound in which only ketone had been reduced (937.5 mg) was obtained, it was reduced by DIBAL again at 0°C for 30 minutes, the same post-treatment was carried out, and compound VIII-3 was obtained 896 mg (81 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 7.40 (d, 2H, J = 8.1 Hz), 7.34 (m, 3H), 7.25 (d, 1H, J = 8.0 Hz), 7.05 (dd, 1H, J = 8.0, 1.8 Hz), 5.80 (s, 1H), 4.68 (s, 2H), 2.15 (brs, 1H), 1.67 (s, 4H), 1.26 (s, 6H), 1.25 (s, 6H).

Alumina 4.70g and PCC 2.65 g (12.3 mmol) were suspended in methanol-free methylene chloride 10 ml under argon replacement, and compound VIII-3, 810mg (2.50 mmol) was dissolved in methanol-free methylene chloride 10 ml, and it was added gradually. 1 hour was allowed to pass, and thereafter the reaction liquid was concentrated, and it was purified using silica gel column chromatography (ethyl acetate : n-hexane = 1 : 7) and compound VIII-4 was obtained 798 mg (99.7 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 10.14 (s, 1H), 8.00 (d, 2H, J = 8.4 Hz), 7.91 (d, 2H, J = 8.1 Hz), 7.80 (d, 1H, J = 1.8 Hz), 7.53 (dd, 1H, J = 8.4, 2.2 Hz), 7.41 (d, 1H, J = 8.1 Hz), 1.73 (s, 4H), 1.32 (s, 6H), 1.30 (s, 6H).

Compound VIII-4, 790mg (2.47 mmol), 2,4-thiazolidinedione 319 mg (2.72 mmol) were suspended in anhydrous toluene 20 ml, and a solution of piperidine 63 mg (0.74 mmol) and acetic acid 45 mg (0.74 mmol) dissolved in anhydrous toluene 8 ml was added, and the mixture was refluxed at 120°C for three hours. The reaction liquid was discharged into iced water, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and after concentration, purification was carried out by silica gel column chromatography (ethyl acetate : hexane = 1 : 2) and TZ221 was obtained 328 mg (32 %).

TZ221: Colorless powder (ethyl acetate / n-hexane); mp 204°C

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 8.46 (s, 1H), 7.90 (d, 2H, J = 8.4 Hz), 7.80 (d, 1H, J = 1.8 Hz), 7.60 (d, 2H, J = 8.1 Hz), 7.53 (dd, 1H, J = 8.0, 1.8 Hz), 7.41 (d, 1H, J = 8.1 Hz), 1.73 (s, 4H), 1.33 (s, 6H), 1.31 (s, 6H),

Anal. Calcd. for C<sub>25</sub>H<sub>25</sub>NO<sub>3</sub>S, C, 71.57, H, 6.01%; N, 3.34%,  
Found, C, 71.28%;H, 5.92%; N, 3.09%.

**Example 22:** Synthesis of TZ223.

1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (VIII-1) and isophthalic acid monomethyl ester chloride were used as starting materials. TZ223 was synthesised according to the process of Example 21.

TZ223: Yellow prisms (ethyl acetate / n-hexane); mp 189°C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 8.46 (brs, 1H), 7.91 (s, 1H), 7.90 (s, 1H), 7.86 (d, 1H, J = 7.7 Hz), 7.81 (d, 1H, J = 1.8 Hz), 7.70 (d, 1H, J = 7.7 Hz), 7.61 (t, 1H, J = 7.7 Hz), 7.52 (dd, 1H, J = 8.1, 1.8 Hz), 7.42 (d, 1H, J = 8.1 Hz), 1.73 (s, 4H), 1.33 (s, 6H), 1.31 (s, 6H),

Anal. Calcd. for C<sub>25</sub>H<sub>25</sub>NO<sub>3</sub>S, C= 71.57%, H= 6.01%, N= 3.34%,  
Found, C= 71.64%, H= 6.16%, N= 3.19%.

**Example 23:** Synthesis of TZ225.

1,2,3,4-tetrahydro-1,1,4,4,6-pentamethyl naphthalene and terephthalic acid monomethyl ester chloride were used as starting materials. TZ225 was synthesised according to the process of Example 21.

TZ225: Yellow prisms (ethyl acetate / n-hexane); mp 245°C

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 8.67 (s, 1H), 7.91 (d, 1H, J = 8.4 Hz), 7.90 (s, 1H), 7.58 (d, 1H, J = 8.8 Hz), 7.26 (s, 1H), 7.21 (s, 1H), 2.33 (s, 3H), 1.70 (s, 4H), 1.32 (s, 6H), 1.22 (s, 6H),

Anal. Calcd. for C<sub>25</sub>H<sub>27</sub>NO<sub>3</sub>S, C= 72.03%, H= 6.28%, N= 3.23%,  
Found, C= 71.87%, H= 6.35%, N = 3.14 %.

**Example 24:** Synthesis of TZ227.

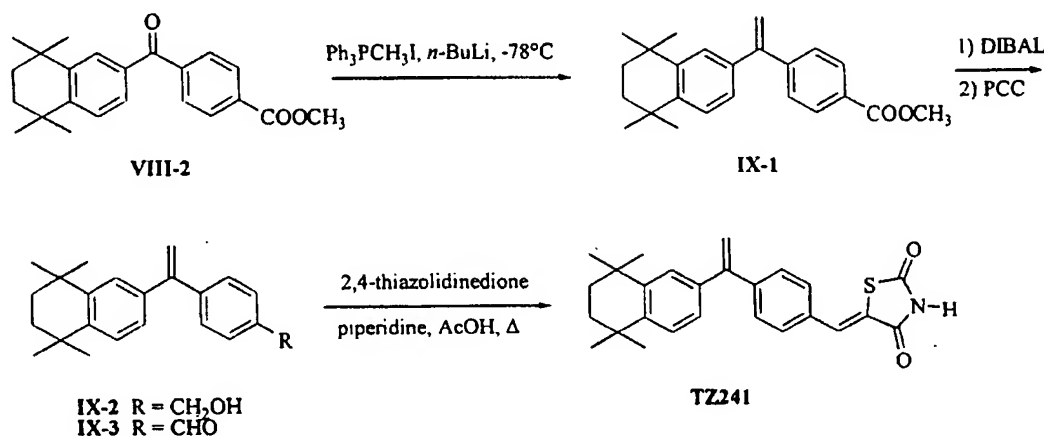
1,2,3,4-tetrahydro-1,1,4,4,6-pentamethyl naphthalene and isophthalic acid monomethyl ester chloride were used as starting materials. TZ227 was synthesised according to the process of Example 21.

TZ227: Pale yellow prisms (ethyl acetate / n-hexane); mp 191°C

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 8.40 (s, 1H), 7.87-7.92 (m, 2H), 7.86 (s, 1H), 7.69 (d, 1H, J = 7.7 Hz), 7.59 (t, 1H, J = 7.7 Hz), 7.25 (s, 1H), 7.23 (s, 1H), 2.32 (s, 3H), 1.71 (s, 4H), 1.33 (s, 6H), 1.22 (s, 6H),

Anal. Calcd. for C<sub>26</sub>H<sub>2</sub>NO<sub>3</sub>S, C= 72.03%, H= 6.28%, N= 3.23%,  
Found, C= 72.21%, H= 6.37%, N= 2.96%.

**Example 25: Synthesis of TZ241.**



Ph<sub>3</sub>PCH<sub>3</sub>I 4.04 g (10.1 mmol) was suspended in 5 mL of THF and n-butyllithium 8.36 ml (13.4 mmol) was added at  $-78^\circ\text{C}$  and was stirred for 15 minutes. Compound VIII-2, 2.35 g (6.71 mmol) was dissolved in 12 mL of THF, and it was added and the mixture was stirred for one hour. Water was added to the reaction liquid, and extraction was carried out with methylene chloride. The organic layer was dewatered with MgSO<sub>4</sub>, and thereafter, it was concentrated, and it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 12.5) and compound IX-1 was obtained 680 mg (30 %).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 8.00 (d, 2H, J = 8.6 Hz), 7.43 (d, 2H, J = 8.4 Hz), 7.26 (d, 1H, J = 8.1 Hz), 7.22 (d, 1H, J = 1.8 Hz), 7.07 (dd, 1H, J = 8.3, 2.2 Hz), 5.53 (d, 1H, J = 1.1 Hz), 5.47 (d, 1H, J = 1.1 Hz), 3.93 (s, 3H), 1.69 (s, 4H), 1.30 (s, 6H), 1.23 (s, 6H).

Compound IX-1, 675 mg (2.01 mmol) was dissolved in THF 5 mL, and DIBAL 6.0 mL (1M toluene solution, 6.0 mmol) was added gradually at  $-78^\circ\text{C}$ , and thereafter it was stirred at  $0^\circ\text{C}$  for 30 minutes. The reaction liquid was discharged into 1N hydrochloric acid and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and it was dewatered with MgSO<sub>4</sub> and thereafter, it was concentrated and thereafter, purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and Compound IX-2 was obtained 619 mg (quantitative).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 7.35 (m, 4H), 7.27 (d, 1H, J = 1.8 Hz), 7.25 (d, 1H, J = 8.4 Hz), 7.08 (dd, 1H, J = 8.4, 2.2 Hz), 5.44 (d, 1H, J = 1.5 Hz), 5.40 (d, 1H, J = 1.1 Hz), 4.72 (s, 2H), 1.69 (s, 4H), 1.29 (s, 6H), 1.24 (s, 6H).

Compound IX-2, 620 mg (2.01 mmol) was dissolved in methanol-free methylene chloride 10 ml, and PCC 866mg (4.02 mmol) was added and the mixture was stirred at room temperature for one hour 30 minutes. The reaction liquid was concentrated, and it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 8) and compound IX-3 was obtained 428.5 mg (70 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 10.03 (s, 1H), 7.85 (d, 2H, J = 8.4 Hz), 7.53 (d, 2H, J = 8.4 Hz), 7.27 (d, 1H, J = 8.1 Hz), 7.23 (d, 1H, J = 1.8 Hz), 7.06 (dd, 1H, J = 8.1, 1.8 Hz), 5.57 (d, 1H, J = 1.1 Hz), 5.51 (d, 1H, J = 0.7 Hz), 1.70 (s, 4H), 1.30 (s, 6H), 1.24 (s, 6H).

Compound XII-4, 420mg (1.37 mmol), 2,4-thiazolidinedione 162 mg (1.38 mmol) were sampled and suspended in anhydrous toluene 8 ml, and a solution of piperidine 32 mg (0.38 mmol) and acetic acid 23 mg (0.38 mmol) dissolved in anhydrous toluene 4 ml was added, and it was refluxed at 120°C for two hours. The reaction liquid was discharged into iced water, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and after concentration, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 4) and TZ241 was obtained 449.2 mg (81 %).

TZ241: Pale yellow needles (ethyl acetate / n-hexane); mp 198°C, <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 8.42 (s, 1H), 7.88 (s, 1H), 7.48 (m, 4H), 7.27 (d, 1H, J = 8.4 Hz), 7.24 (d, 1H, J = 1.8 Hz), 7.06 (dd, 1H, J = 8.4, 1.8 Hz), 5.52 (s, 1H), 5.51 (s, 1H), 1.70 (s, 4H), 1.30 (s, 6H), 1.25 (s, 6H), .  
Anal. Calcd. for C<sub>26</sub>H<sub>27</sub>NO<sub>2</sub>S, C= 74.79%, H= 6.52%, N= 3.35%,  
Found C= 74.59%, H= 6.51%, N = 3-32%.

**Example 26:** Synthesis of TZ243.

m-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoyl) benzoic acid methyl ester was used as the starting material, and TZ243 was synthesised according to the process of Example 25.

TZ243: Colorless powder (ethyl acetate / n-hexane); mp 168°C

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 8.30 (brs, 1H), 7.85 (s, 1H), 7.46 (m, 4H), 7.28 (d, 1H, J = 8.1 Hz), 7.25 (d, 1H, J = 2.2 Hz), 7.05 (dd, 1H, J = 8.1Hz, 2.2 Hz), 5.51 (d, 1H, J = 0.7 Hz), 5.46 (d, 1H, J = 1.1 Hz), 1.70 (s, 4H), 1.33 (s, 6H), 1.25 (s, 6H),  
Anal. Calcd. for C<sub>26</sub>H<sub>27</sub>NO<sub>2</sub>S•1/4H<sub>2</sub>O, C= 74.00%, H= 6.57%, N= 3.32%,  
Found C= 74.00%, H= 6.60%, N= 3.36%.

**Example 27:** Synthesis of TZ245.

Ph<sub>3</sub>PCH<sub>3</sub>I 1.09 g (2.70 mmol) was suspended in 5 mL of THF and n-butyllithium 2.22 ml (3.56 mmol) was added at -78°C and was stirred for 15 minutes. TZ225 (cf. Example 23) 800 mg (1.78

mmol) was dissolved in 6 mL of THF, and it was added and the mixture was stirred for one hour. Water was added to the reaction liquid and extraction was carried out with methylene chloride. The organic layer was dewatered with  $\text{MgSO}_4$ , and thereafter, it was concentrated, and it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and TZ245 was obtained 52 mg (6.5 %).

TZ245: Pale yellow powder (ethyl acetate / n-hexane); mp 281°C

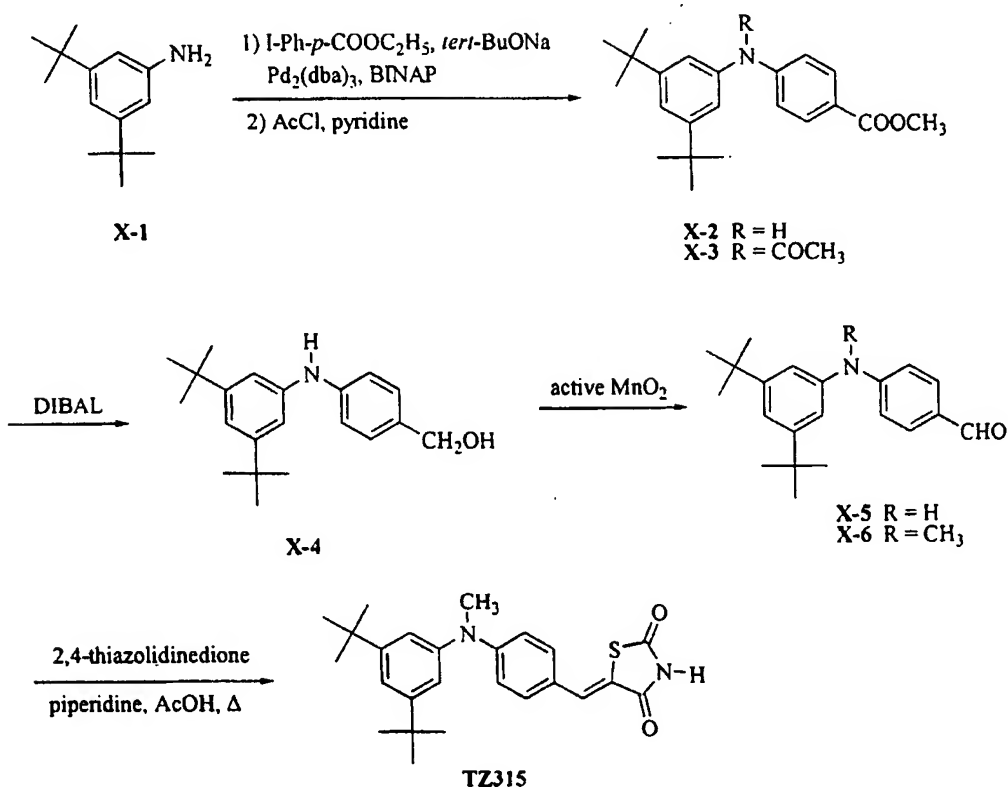
$^1\text{H}$ -NMR (400MHz,  $\text{CDCl}_3$ ) 8.29 (s, 1H), 7.84 (s, 1H), 7.42 (m, 4H), 7.12 (s, 1H), 7.09 (s, 1H), 5.83 (d, 1H, J = 1.1 Hz), 5.32 (d, 1H, J = 1.1 Hz), 1.96 (s, 3H), 1.70 (s, 4H), 1.31 (s, 6H), 1.28 (s, 6H),  
Anal. calcd. for  $\text{C}_{27}\text{H}_{29}\text{NO}_2\text{S}$ , C= 75.14%, H= 6.77%, N= 3.25%,  
Found C= 74.86%, H= 6.81%, N= 3.33 %.

**Example 28:** Synthesis of TZ247.

m-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthoyl) benzoic acid methyl ester was used as the starting material, and TZ247 was synthesised according to the process of Example 25.

TZ247: Pale yellow powder (ethyl acetate / n-hexane); mp 185°C,  $^1\text{H}$ -NMR (400MHz,  $\text{CDCl}_3$ ) 8.19 (brs, 1H), 7.79 (s, 1H), 7.49 (d, 1H, J = 7.7 Hz), 7.43 (t, 1H, J = 7.7 Hz), 7.37 (d, 1H, J = 7.7 Hz), 7.25 (s, 1H), 7.13 (s, 1H), 7.12 (s, 1H), 5.80 (d, 1H, J = 1.1 Hz), 5.31 (d, 1H, J = 1.1 Hz), 1.96 (s, 3H), 1.72 (s, 4H), 1.32 (s, 6H), 1.29 (s, 6H),  
Anal. Calcd. for  $\text{C}_{27}\text{H}_{29}\text{NO}_2\text{S}$ , C= 75.14%, H= 6.77%, N= 3.25%,  
Found C= 74.85%, H= 6.72%, N= 2.98%.

**Example 29: Synthesis of TZ315.**



3,5-di-tert-butyl aniline (X-1) 1.00 g (4.88 mmol), 4-iodobenzoic acid ethyl 1.37 g (4.95 mmol), tert-BuONa 549mg (5.68 mmol) were dissolved in anhydrous toluene 15 ml, and, under argon replacement, tris (dibenzylideneacetone) dipalladium(0) 91 mg, (R)-BINAP 139mg (0.22 mmol) were introduced, and the mixture was stirred at 100°C for one hour. It was cooled to room temperature, and thereafter, extraction was carried out with ether. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 6) and Compound X-2 was obtained 0.94 g (55 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 7.92 (d, 2H, J = 8.8 Hz), 7.14 (t, 1H, J = 1.8 Hz), 7.02 (d, 2H, J = 1.8 Hz), 6.96 (d, 2H, J = 8.8 Hz), 4.33 (q, 2H, J = 7.3 Hz), 1.37 (t, 3H, J = 7.3 Hz), 1.32 (s, 18H).

Compound X-2, 935mg (2.65 mmol) was dissolved in anhydrous benzene 10 ml, and acetyl chloride 249 mg (3.18 mmol), anhydrous pyridine 0.5 ml were added, and the mixture was stirred at room temperature for five hours. Iced water was added to the reaction liquid, and extraction was carried out with ethyl acetate. The organic layer was washed with dilute hydrochloric acid, aqueous sodium chloride, and it was dewatered with MgSO<sub>4</sub>, and after concentration, it was purified by

silica gel column chromatography (ethyl acetate : n-hexane = 1 : 4) and Compound X-3 was obtained 956 mg (92 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 7.99 (d, 2H, J = 8.4 Hz), 7.39 (s, 1H), 7.34 (d, 2H, J = 8.8 Hz), 7.05 (d, 2H, J = 1.8 Hz), 4.35 (q, 2H, J = 7.3 Hz), 2.04 (s, 3H), 1.37 (t, 1H, J = 7.0 Hz), 1.30 (s, 18H).

Compound X-3, 950mg (2.40 mmol) was dissolved in THF 8 mL under argon replacement, and DIBAL 7.2 mL (1M toluene solution, 7.20 mmol) was added dropwise gradually while stirring at -78°C. The reaction liquid was discharged into 2N hydrochloric acid, and, after 15 minutes, extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and after concentration, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and Compound X-4 was obtained 412 mg (55 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 7.27 (m, 3H), 7.04 (m, 3H), 6.96 (d, 2H, J = 1.5 Hz), 4.61 (s, 2H), 1.31 (s, 18H).

Compound X-4, 400mg (1.29 mmol) was dissolved in methanol-free methylene chloride 8 ml, and active MnO<sub>2</sub> 1.32g (85 %, 12.9 mmol) was added, and the mixture was stirred at room temperature for 12 hours. The reaction liquid was filtered, thereafter the filtrate was concentrated, and it was purified by silica gel column chromatography (1 : 4) and Compound X-5 was obtained 184 mg (46 %).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 9.78 (s, 1H), 7.74 (d, 2H, J = 8.8 Hz), 7.20 (t, 1H, J = 1.8 Hz), 7.05 (d, 1H, J = 1.8 Hz), 6.99 (d, 2H, J = 8.4 Hz), 6.17 (s, 1H), 1.33 (s, 18H).

NaH 34mg (60 %, 0.87 mmol) was washed with n-hexane, and it was suspended in DMF 1 ml. Compound X-5, 180mg (0.58 mmol) was dissolved in DMF 5 ml, and it was added and the mixture was stirred at room temperature for 15 minutes. CH<sub>3</sub>I 0.14 ml (2.25 mmol) was added to this mixture and further was stirred for one hour. The DMF was eliminated by distillation, and water was added to the residue and extraction was carried out with methylene chloride. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 6) and Compound X-6 was obtained 173 mg (92 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 9.75 (s, 1H), 7.68 (d, 2H, J = 8.8 Hz), 7.33 (t, 1H, J = 1.8 Hz), 7.05 (d, 2H, J = 1.8 Hz), 6.74 (d, 2H, J = 8.8 Hz), 3.40 (s, 3H), 1.33 (s, 18H).

Compound X-6, 170mg (0.53 mmol) and 2,4-thiazolidinedione 62 mg (0.53 mmol) were suspended in anhydrous toluene 4 ml, and a solution of piperidine 13.4 mg (0.16 mmol) and acetic acid 9.5 mg (0.16 mmol) dissolved in anhydrous toluene 1.6 ml was added, and the mixture was refluxed at 120°C for one hour 30 minutes. The reaction liquid was discharged into iced water and extraction

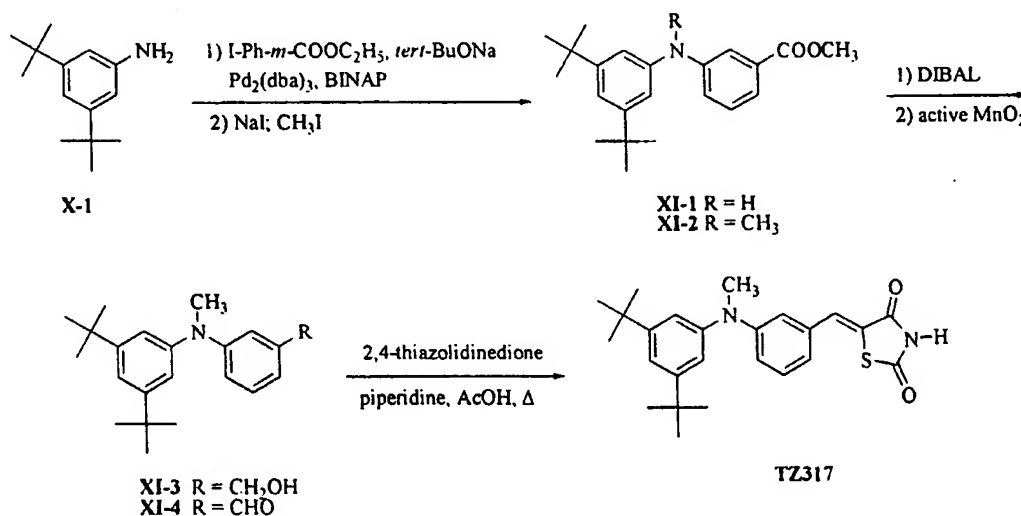
was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with  $\text{MgSO}_4$ , and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and TZ315 was obtained 197 mg (89 %).

TZ315: Yellow needles (ethyl acetate / n-hexane); mp  $254^\circ\text{C}$ ,  $^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ) 8.11 (brs, 1H), 7.77 (s, 1H), 7.34 (m, 3H), 7.04 (d, 1H,  $J = 1.8$  Hz), 6.77 (d, 2H,  $J = 8.8$  Hz), 3.39 (s, 3H), 1.33 (s, 18H),

Anal. Calcd. for  $\text{C}_{25}\text{H}_{30}\text{N}_2\text{O}_2\text{S}$ , C= 71.06%, H= 7.16%, N= 6.63%;

Found C= 70.96%, H= 7.17%, N= 6.81%.

**Example 30: Synthesis of TZ317.**



3-iodobenzoic acid methyl 1.37 g (5.23 mmol), 3,5-di-tert-butyl aniline (X-1) 1.00 g (4.88 mmol), tert-BuONa 549mg (5.68 mmol) were dissolved in anhydrous toluene 15 ml, and, under argon replacement, tris (dibenzylideneacetone) dipalladium(0) 91 mg, (R)-BINAP 139mg (0.22 mmol) were introduced, and the mixture was stirred at  $80^\circ\text{C}$  for one hour. It was cooled to room temperature, and thereafter, it was extracted with ether. The organic layer was washed with aqueous sodium chloride, and was dewatered with  $\text{MgSO}_4$ , and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 8) and Compound XI-1 (crude product) was obtained 514 mg (31 %).

$^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ) 7.87 (d, 1H,  $J = 7.7$  Hz), 7.75 (m, 1H), 7.53 (m, 1H), 7.29 (t, 1H,  $J = 7.7$  Hz), 7.07 (t, 1H,  $J = 1.5$  Hz), 6.98 (d, 2H,  $J = 1.5$  Hz), 3.88 (s, 3H), 1.32 (s, 18H).

NaH 88mg (60 %, 2.21 mmol) was washed with n-hexane, and it was suspended in DMF 1 ml. Compound XI-1 (crude product) 500 mg (1.47 mmol) was dissolved in DMF 8 ml, and it was added

and the mixture was stirred at room temperature for 15 minutes. Methyl iodide 0.35 ml (5.62 mmol) was added and the mixture was stirred for three hours. The DMF was eliminated by distillation, water was added to the residue and it was extracted with methylene chloride. The organic layer was washed in aqueous sodium chloride. It was dewatered with  $\text{MgSO}_4$ , thereafter, the solvent was eliminated by distillation, thereafter the residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 10) and Compound XI-2 was obtained 180 mg (34.5 %).

$^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ) 7.60 (m, 1H), 7.47 (d, 1H,  $J = 7.7$  Hz), 7.23 (t, 1H,  $J = 8.0$  Hz), 7.17 (t, 1H,  $J = 1.8$  Hz), 7.04 (m, 1H), 6.99 (d, 2H,  $J = 1.8$  Hz), 3.92 (s, 3H), 3.88 (s, 3H), 1.30 (s, 18H).

Compound XI-2, 170mg (0.48 mmol) was dissolved in THF 4 mL under argon replacement, and DIBAL 1.44 mL (1M toluene solution, 1.44 mmol) was added dropwise gradually while stirring at  $-78^\circ\text{C}$ . After 30 minutes, it was discharged into 2N hydrochloric acid, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with  $\text{MgSO}_4$ , and thereafter the solvent was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and Compound XI-3 was obtained 130 mg (83 %).

$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 7.20 (t, 1H,  $J = 1.8$  Hz) 7.14 (t, 1H,  $J = 1.8$  Hz), 6.98 (d, 2H,  $J = 1.8$  Hz), 6.92 (s, 1H), 6.81 (d, 2H,  $J = 8.1$  Hz), 4.62 (d, 2H,  $J = 5.9$  Hz), 3.34 (s, 3H), 1.30 (s, 18H).

Compound XI-3, 125 mg (0.38 mmol) was dissolved in methanol-free methylene chloride 4 ml, and active  $\text{MnO}_2$  394mg (85 %, 3.85 mmol) was added, and the mixture was stirred at room temperature for six hours 30 minutes. The reaction liquid was filtered, the filtrate was concentrated, thereafter, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 6) and Compound XI-4 was obtained 43.5 mg (35 %) (XI-3 is recovered 51 mg).

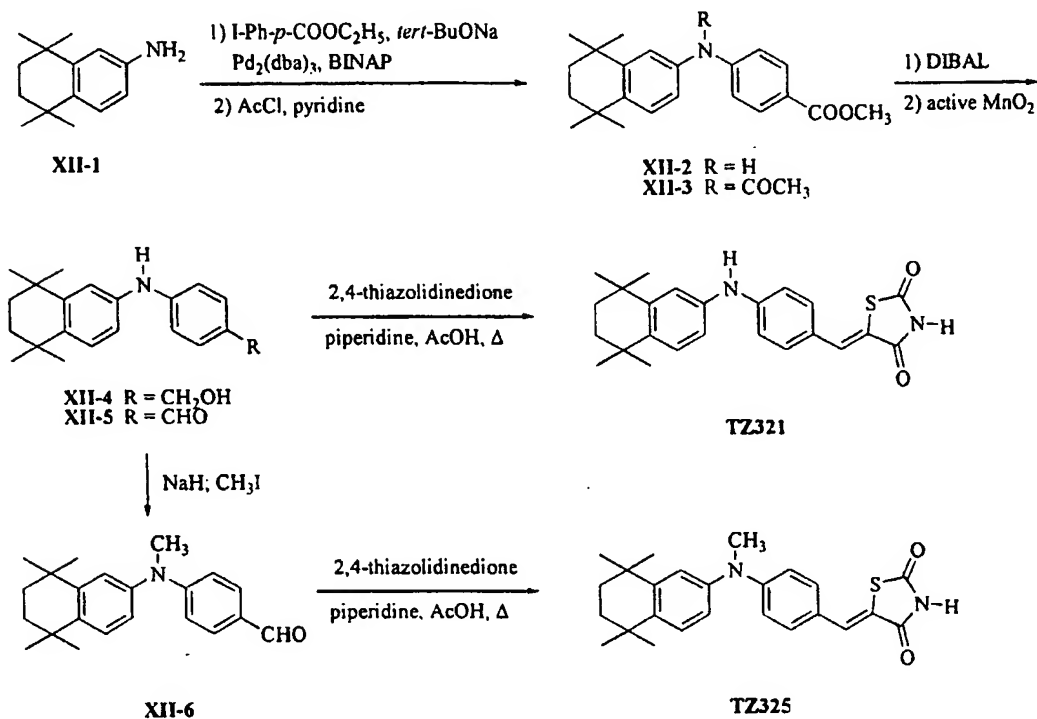
$^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ) 9.92 (s, 1H), 7.35 (m, 1H), 7.32 (t, 1H,  $J = 7.7$  Hz), 7.27 (m, 1H), 7.23 (t, 1H,  $J = 1.8$  Hz), 7.07 (m, 1H), 7.02 (d, 1H,  $J = 1.8$  Hz), 3.37 (s, 3H), 1.31 (s, 18H).

Compound XI-4, 65 mg (0.20 mmol), 2,4-thiazolidinedione 23 mg (0.20 mmol) were suspended in anhydrous toluene 3 ml. A solution of piperidine 5.1 mg (0.060 mmol) and acetic acid 3.6 mg (0.060 mmol) dissolved in anhydrous toluene 0.6 ml was added, and the mixture was refluxed at  $120^\circ\text{C}$  for three hours 30 minutes. The reaction liquid was discharged into iced water, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with  $\text{MgSO}_4$ , and thereafter the solvent was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and TZ317 was obtained 88 mg (quantitative).

TZ317: Yellow needles (ethyl acetate / n-hexane); mp  $234^\circ\text{C}$

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 8.41 (brs, 1H), 7.77 (s, 1H), 7.22-7.57 (m, 2H), 7.01 (d, 2H, J = 1.5 Hz), 6.89 (dd, 2H, J = 8.1, 2.2 Hz), 6.83 (t, 1H, J = 1.6 Hz), 3.35 (s, 3H), 1.32 (s, 18H),  
Anal. Calcd. for C<sub>25</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>S, C = 71.06%, H = 7.16%, N = 6.63%,  
Found C = 70.88%, H = 7.09%, N = 6.36 %.

**Example 31: Synthesis of TZ321.**



2-amino-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene (XII-1) 1.50 g (7.39 mmol), 4-iodobenzoic acid ethyl 1.70 g (6.16 mmol), tert-BuONa 0.83 g (8.62 mmol) were dissolved in anhydrous toluene 30 ml, and, under argon replacement, tris (dibenzylideneacetone) dipalladium(0) 138 mg (0.15 mmol) and (R)-BINAP 210mg (0.33 mmol) were added to this mixture and stirred at 80°C. One hour was allowed to pass, the reaction liquid was cooled to room temperature and was extracted with ether, and the organic layer was washed with aqueous sodium chloride. It was dewatered with MgSO<sub>4</sub>, and after concentration, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 8) and Compound XII-2 was obtained 1.38 g (64 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 7.90 (d, 2H, J = 8.8 Hz), 7.26 (d, 2H, J = 8.4 Hz), 7.10 (d, 1H, J = 2.5 Hz), 6.96 (dd, 1H, J = 8.4, 2.6 Hz), 6.93 (d, 2H, J = 8.8 Hz), 4.33 (q, 2H, J = 7.0 Hz), 1.69 (s, 4H), 1.37 (t, 3H, J = 7.0 Hz), 1.28 (s, 6H), 1.27 (s, 6H).

Compound XII-2, 1.95 g (5.56 mmol) was dissolved in anhydrous pyridine 10 ml, and acetyl chloride 523 mg (6.67 mmol) was added and the mixture was stirred at room temperature for three hours. Iced water was added, and the mixture was extracted with ethyl acetate, and the organic layer was washed with dilute hydrochloric acid, aqueous sodium chloride. It was dewatered with  $\text{MgSO}_4$ , and after concentration, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and Compound XII-3 was obtained 1.34 g (61.5 %).

$^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ) 8.00 (d, 2H, J = 8.4 Hz), 7.32 (d, 2H, J = 8.8 Hz), 7.31 (d, 1H, J = 8.8 Hz), 7.14 (d, 1H, J = 2.2 Hz), 6.95 (dd, 1H, J = 8.4, 2.2 Hz), 4.35 (q, 2H, J = 6.9 Hz), 2.05 (s, 3H), 1.69 (s, 4H), 1.37 (t, 3H, J = 6.9 Hz), 1.28 (s, 6H), 1.24 (s, 6H).

Compound XII-3, 1.34 g (3.41 mmol) was dissolved in THF 6 mL, and DIBAL 10.2 mL (1.0M toluene solution, 10.2 mmol) was added gradually at  $-78^\circ\text{C}$ . 1 hour was allowed to pass, thereafter, it was discharged into 1N hydrochloric acid, and extraction was carried out with ethyl acetate. The organic layer was dewatered with  $\text{MgSO}_4$ , and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and Compound XII-4 was obtained 621 mg (59 %).

$^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ) 7.24 (d, 2H, J = 8.4 Hz), 7.03 (d, 1H, J = 2.2 Hz), 7.00 (d, 2H, J = 8.4 Hz), 6.89 (dd, 1H, J = 8.4, 2.2 Hz), 4.60 (s, 2H), 1.68 (s, 4H), 1.27 (s, 6H), 1.26 (s, 6H).

Compound XII-4, 615mg (2.0 mmol) was dissolved in methanol-free methylene chloride 8 ml, and active  $\text{MnO}_2$  2.05g (85 %, 20.0 mmol) was added, and the mixture was stirred at room temperature for 16 hours. The reaction liquid was filtered, thereafter, the filtrate was concentrated, and it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 4) and Compound XII-5 was obtained 271 mg (44 %).

$^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ) 9.78 (s, 1H), 7.73 (d, 2H, J = 8.8 Hz), 7.29 (d, 1H, J = 8.4 Hz), 7.11 (d, 1H, J = 2.2 Hz), 6.99 (m, 3H), 1.70 (s, 4H), 1.29 (s, 6H), 1.28 (s, 6H).

Compound XII-5, 150mg (0.49 mmol) and 2,4-thiazolidinedione 63 mg (0.54 mmol) were suspended in anhydrous toluene 6 ml, and a solution of piperidine 12.7 mg (0.15 mmol) and acetic acid 8.9 mg (0.15 mmol) dissolved in anhydrous toluene 1.5 ml was added, and the mixture was refluxed at  $120^\circ\text{C}$  for 30 minutes. The reaction liquid was discharged into iced water, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with  $\text{MgSO}_4$ , thereafter, it was concentrated, and TZ321 was obtained 178 mg (90 %).

TZ321: Orange needles (ethyl acetate / n-hexane); mp  $297^\circ\text{C}$

<sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>, 30°C) 8.69 (s, 1H), 7.65 (s, 1H), 7.42 (d, 2H, J = 8.8 Hz), 7.26 (d, 1H, J = 8.8 Hz), 7.07 (d, 1H, J = 2.6 Hz), 7.06 (d, 2H, J = 8.4 Hz), 6.98 (dd, 1H, J = 8.4, 2.6 Hz), 1.64 (s, 4H), 1.24 (s, 6H), 1.24 (s, 6H),

Anal. Calcd. for C<sub>24</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>S, C= 70.91%, H= 6.45%, N= 6.89%,

Found, C= 71.06%, H= 6.42%, N= 6.88 %.

**Example 32: Synthesis of TZ325.**

NaH 20mg (60 %, 0.49 mmol) was washed with little amount of n-hexane, and it was suspended in DMF 1 ml. Compound XII-5, 100mg (0.33 mmol) was dissolved in 4 mL of DMF and it was added to this suspension, and the mixture was stirred at room temperature for 20 minutes. CH<sub>3</sub>I 0.08 mL (1.28 mmol) was added to this mixture, and the mixture was stirred for 30 minutes. DMF was distilled under reduced pressure and water was added to the residue and was extracted with methylene chloride. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 5) and Compound XII-6 was obtained 80 mg (76.59%).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 9.75 (s, 1H), 7.68 (d, 2H, J = 9.2 Hz), 7.34 (d, 1H, J = 8.4 Hz), 7.14 (d, 1H, J = 2.2 Hz), 6.96 (dd, 1H, J = 8.4, 2.2 Hz), 6.76 (d, 2H, J = 9.2 Hz), 3.37 (s, 3H), 1.71 (s, 4H), 1.31 (s, 6H), 1.26 (s, 6H).

Compound XII-6, 75mg (0.23 mmol), 2,4-thiazolidinedione 30 mg (0.26 mmol) were suspended in anhydrous toluene 4 ml, and a solution of piperidine 6.0 mg (0.07 mmol) and acetic acid 12 mg (0.07 mmol) dissolved in anhydrous toluene 0.75 ml was added, and the mixture was refluxed at 120°C. The reaction liquid was discharged into iced water, and, after 30 minutes, extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and it was dewatered at MgSO<sub>4</sub>, and thereafter, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and TZ325 was obtained 105 mg (quantitative).

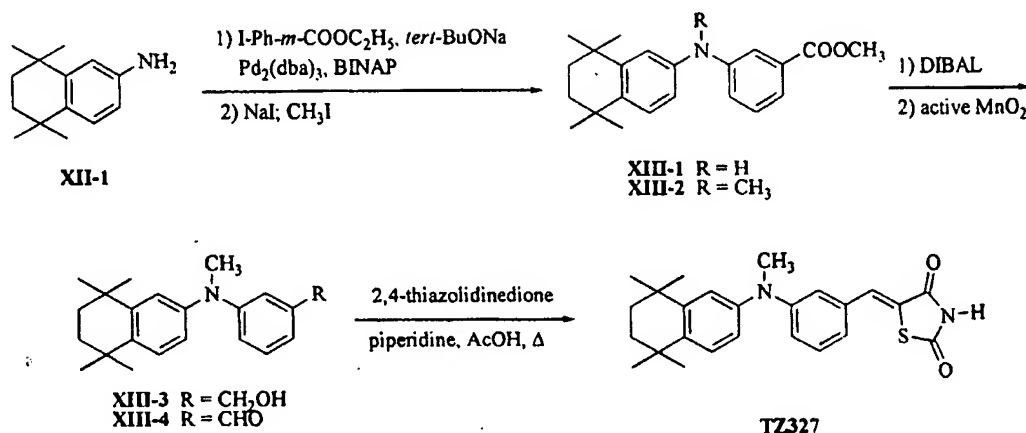
TZ325: Yellow powder (ethyl acetate / n-hexane); mp 238°C

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 8.29 (s, 1H), 7.77 (s, 1H), 7.33 (d, 2H, J = 8.2 Hz), 7.33 (d, 1H, J = 8.4 Hz), 7.13 (d, 1H, J = 2.6 Hz), 6.95 (dd, 1H, J = 8.4, 2.6 Hz), 6.79 (d, 2H, J = 8.8 Hz), 3.36 (s, 3H), 1.71 (s, 4H), 1.31 (s, 6H), 1.26 (s, 6H),

Anal. Calcd. for C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S, C= 71.40%, H= 6.71%, N= 6.66%,

Found, C= 71.51%, H= 6.70%, N= 6.60 %.

**Example 33: Synthesis of TZ327.**



3-iodobenzoic acid methyl 1.24 g (4.73 mmol), 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylamine 1.03 g (5.07 mmol), tert-BuONa 571mg (5.92 mmol) were dissolved in anhydrous toluene 30 ml, and, under argon replacement, tris (dibenzylideneacetone) dipalladium(0) 117 mg (0.13 mmol), (R)-BINAP 177mg (0.28 mmol) were introduced, and the mixture was stirred at 80°C for one hour. The reaction liquid was cooled to room temperature, and extraction was carried out with ether. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and after concentration, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 8) and Compound XIII-1 was obtained 877 mg (55 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 7.70 (t, 1H, 2.0 Hz), 7.50 (d, 1H, J = 7.7 Hz), 7.28 (t, 1H, J = 7.9 Hz), 7.23 (d, 1H, J = 8.4 Hz), 7.17 (dd, 1H, J<sub>H</sub>8.1, 1.5 Hz), 7.06 (d, 1H, J = 2-2 Hz), 6.90 (dd, 1H, J = 8.4, 2.2 Hz), 3.89-(s, 3H), 1.69 (s, 4H), 1.28 (s, 6H), 1.27 (s, 6H).

NaH 72mg (60 %, 1.78 mmol) was washed with n-hexane, and it was suspended in dried DMF 1 ml, and Compound XIII-1, 400mg (1.19 mmol) was dissolved in DMF 10 ml, and it was added, and the mixture was stirred at room temperature. After 20 minutes, methyl iodide 0.28 ml (4.50 mmol) was added, and the mixture was stirred for 40 minutes. The DMF was eliminated by distillation and water was added and the mixture was extracted with methylene chloride. The organic layer was washed with aqueous sodium chloride, and after elimination of the solvent, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 8) and Compound XIII-2 was obtained 371.5 mg (94.5 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 7.60 (t, 1H, 2.0 Hz), 7.47 (d, 1H, 7.7 Hz), 7.25 (d, 1H, 8.4 Hz), 7.22 (d, 1H, 7.7 Hz), 7.08 (d, 1H, 2.6 Hz), 7.05 (dd, 1H, 8.4, 2.7 Hz), 6.88 (dd, 1H, 8.4Hz, 2.6 Hz), 3.88 (s, 3H), 3.33 (s, 3H), 1.68 (s, 4H), 1.29 (s, 6H), 1.24 (s, 6H).

Compound XIII-2, 570mg (1.62 mmol) was dissolved in THF 7 mL under argon replacement, and DIBAL 4.87 mL (1M toluene solution, 4.87 mmol) was added dropwise gradually while stirring this solution at  $-78^{\circ}\text{C}$ . The reaction liquid was discharged into 2N hydrochloric acid, and, after 30 minutes, extraction was carried out with ethyl acetate. The organic layer was washed with 2N hydrochloric acid, saturated aqueous sodium bicarbonate solution, aqueous sodium chloride, and it was dewatered with  $\text{MgSO}_4$ , and after concentration, purification was carried out by silica gel column chromatography (1 : 3) and Compound XIII-3 was obtained 500 mg (91 %).

$^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ) 7.23 (d, 1H, 8.3 Hz), 7.19 (d, 1H, 8.1 Hz), 7.06 (d, 1H, 2.6 Hz), 6.94 (m, 1H), 6.88 (dd, 1H, 8.4, 2.2 Hz), 6.84 (m, 2H), 4.62 (s, 2H), 3.31 (s, 3H), 1.68 (s, 4H), 1.29 (s, 6H), 1.24 (s, 6H).

Compound XIII-3, 100mg (0.30 mmol) was dissolved in methanol-free methylene chloride 4 ml, and active  $\text{MnO}_2$  303mg (85 %, 2.97 mmol) was added, and the mixture was stirred at room temperature for 24 hours. The reaction liquid was filtered, and filtrate was concentrated, and thereafter, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 9) and Compound XIII-4 was obtained 71.6 mg (72 %).

$^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ) 9.92 (s, 1H), 7.27-7.38 (m, 4H), 7.10 (d, 1H, 2.6 Hz), 7.06-7.09 (m, 1H), 6.92 (dd, 1H, 8.4, 2.2 Hz), 3.34 (s, 3H), 1.69 (s, 4H), 1.30 (s, 6H), 1.24 (s, 6H).

Compound XIII-4, 220mg (0.66 mmol), 2,4-thiazolidinedione 84 mg (0.72 mmol) were suspended in anhydrous toluene 6 ml, and a solution of piperidine 17 mg (0.20 mmol) and acetic acid 12 mg (0.20 mmol) dissolved in anhydrous toluene 2 ml was added, and the mixture was refluxed at  $120^{\circ}\text{C}$  for one hour. The reaction liquid was discharged into iced water and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with  $\text{MgSO}_4$ , and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and TZ327 was obtained 312 mg (quantitative).

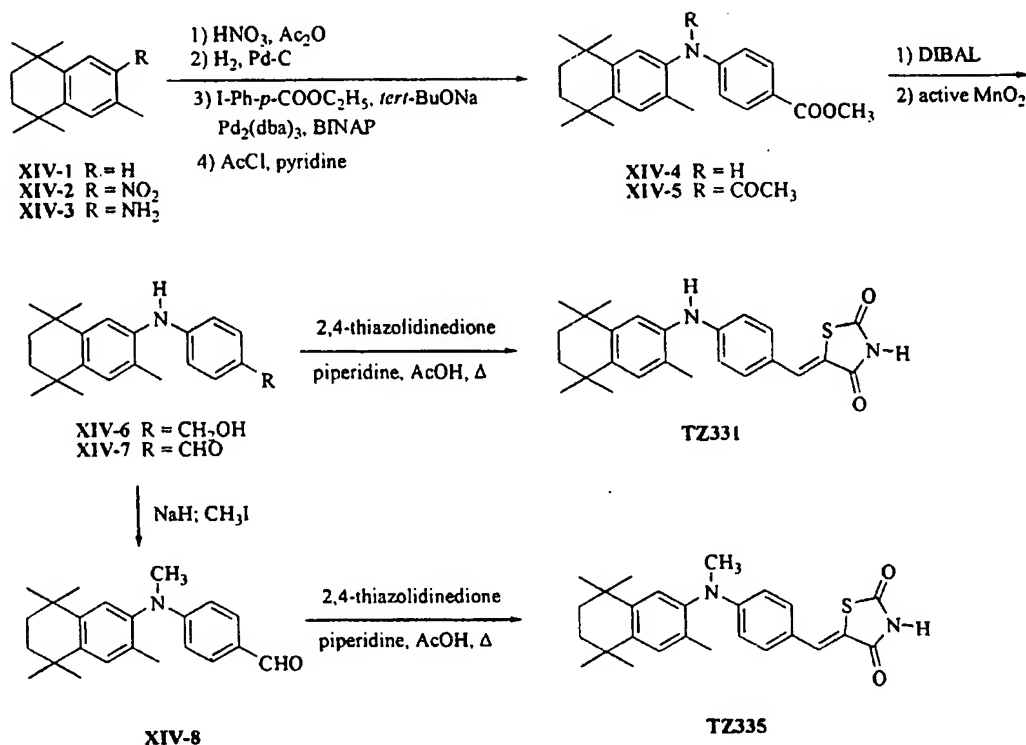
TZ327: Orange prisms (ethyl acetate / n-hexane); mp  $196^{\circ}\text{C}$ ,

$^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ) 8.39 (s, 3H) 7.76 (s, 3H) 7.31 (d, 1H, 8.4 Hz) 7.27 (d, 1H, 8.4 Hz) 7.10 (d, 1H, 2.2 Hz) 6.92 (dd, 1H, 8.4Hz, 2.2 Hz) 6.89 (d, 2H, 7.0 Hz) 6.83 (t, 1H, 2.0 Hz) 3.32 (s, 3H) 1.71 (s, 4H) 1.31 (s, 6H) 1.26 (s, 6H),

Anal. Calcd. for  $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_2\text{S}$ , C= 71.40%, H= 6.71%, N= 6.66%,

Found, C= 71.15%, H= 6.61%, N = 6.44 %.

Example 34: Synthesis of TZ331.



1,2,3,4-tetrahydro-1,1,4,4,6-pentamethyl naphthalene 2.69 g (13.3 mmol) was dissolved in acetic anhydride 20 ml, and it was cooled to 0°C. 61 % nitric acid 0.74 ml (16.0 mmol) was added gradually to this solution. 2 hours were allowed to pass, and thereafter the reaction liquid was discharged into iced water, it was neutralized with sodium hydroxide, and thereafter, extraction was carried out with ether. The organic layer was shaken with aqueous sodium chloride and dewatered with MgSO<sub>4</sub>, thereafter, it was concentrated, and Compound XIV-2 was obtained 3.03 g (92 %).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 7.96 (s, 1H), 7.21 (s, 1H), 2.56 (s, 3H), 1.70 (s, 4H), 1.30 (s, 6H), 1.29 (s, 6H)

Compound XIV-2, 3.02 g (12.2 mmol) was dissolved in ethyl acetate 20 ml, ethanol 30 ml, and Pd/C 400 mg was added, and catalytic reduction was carried out with hydrogen at room temperature. Six hours 30 minutes was allowed to pass, thereafter, catalyst was eliminated by filtration, and filtrate was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 4) and Compound XIV-3 was obtained 1.48 g (56 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 6.97 (s, 1H), 6.61 (s, 1H), 3.45 (brs, 2H), 2.14 (s, 3H), 1.64 (s, 4H), 1.24 (s, 6H), 1.24 (s, 6H).

4-iodobenzoic acid methyl 3.82 g (13.8 mmol), Compound XIV-3, 3.00 g (13.8 mmol) and tert-BuONa 1.55 g (16.1 mmol) were dissolved in anhydrous toluene 30 ml, and, under argon replacement, tris (dibenzylideneacetone) dipalladium(0) 320 mg (0.35 mmol), (R)-BINAP 480mg (0.77 mmol) were added, and the mixture was stirred at 100°C for three hours. The reaction liquid was cooled to room temperature and extraction was carried out with ether. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and after concentration, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 10) and Compound XIV-4 was obtained 2.04 g (40 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 7.89 (d, J = 8.8Hz, 2H), 7.21 (s, 1H), 7.18 (s, 1H), 6.76 (d, J = 8.8Hz, 2H), 4.32 (q, J = 7.0Hz, 2H), 2.19 (s, 3H), 1.68 (s, 4H), 1.37 (t, J = 7.0 Hz, 3H), 1.29 (s, 6H), 1.24 (s, 6H).

Compound XIV-4, 2.03 g (5.56 mmol) was dissolved in anhydrous benzene 30 ml, and acetyl chloride 524 mg (6.67 mmol) and anhydrous pyridine 1 ml were added, and the mixture was stirred at room temperature for two hours. Acetyl chloride 0.20 ml was further added to the reaction liquid and it was stirred at 50°C for four hours and furthermore at 60°C for 23 hours. Iced water was added to the reaction liquid and extraction was carried out with ethyl acetate. The organic layer was washed with 2N hydrochloric acid and aqueous sodium chloride, and it was dewatered with MgSO<sub>4</sub>, and thereafter, it was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 4) and Compound XIV-5 was obtained 1.66 g (62 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 7.97 (d, J = 8.8Hz, 2H), 7.33 (d, J = 8.8Hz, 2H), 7.17 (s, 1H), 7.13 (s, 1H), 4.34 (q, J = 7.0Hz, 2H), 2.06 (s, 3H), 1.97 (s, 3H), 1.69 (s, 4H), 1.36 (t, J = 7.0 Hz, 3H), 1.29 (s, 6H), 1.26 (s, 6H).

Compound XIV-5, 1.62 g (3.98 mmol) was dissolved in THF 10 mL under argon replacement, and DIBAL 11.9 mL (1M toluene solution, 11.9 mmol) was added slowly dropwise while stirring this solution at -78°C. After 30 minutes, the reaction liquid was discharged into 2N hydrochloric acid, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and Compound XIV-6 was obtained 0.99 g (77 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 7.23 (d, J = 8.4Hz, 2H), 7.19 (s, 1H), 7.12 (s, 1H), 6.87 (d, J = 8.4Hz, 2H), 5.33 (s, 1H), 4.60 (d, J = 5.5Hz, 2H), 2.20 (s, 3H), 1.67 (s, 4H), 1.51 (t, J = 5.6 Hz, 1H), 1.28 (s, 6H), 1.22 (s, 6H).

Compound XIV-6, 985mg (3.05 mmol) was dissolved in methanol-free methylene chloride 14 ml, and active MnO<sub>2</sub> 3.11g (85 %, 30.5 mmol) was added, and the mixture was stirred at room

temperature for 22 hours. The reaction liquid was filtered, and the filtrate was concentrated, and thereafter, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 4) and Compound XIV-6 was obtained 297 mg (30 %, raw material recovered 282 mg).

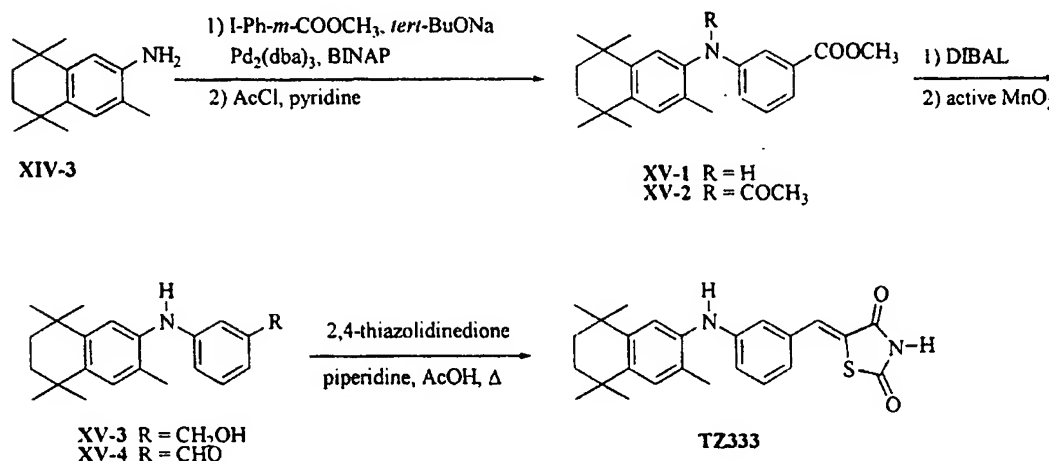
<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 9.76 (s, 1H), 7.71 (d, J = 8.8Hz, 2H), 7.20 (s, 1H), 7.18 (s, 1H), 6.78 (d, J = 8.4 Hz, 2H), 5.80 (s, 1H), 2.05 (s, 3H), 1.69 (s, 4H), 1.30 (s, 6H), 1.25 (s, 6H).

Compound XIV-6, 70mg (0.22 mmol), 2,4-thiazolidinedione 25.5 mg (0.22 mmol) were suspended in anhydrous toluene 4 ml, and a solution of piperidine 5.6 mg (0.065 mmol) and acetic acid 3.9 mg (0.065 mmol) dissolved in anhydrous toluene 0.67 ml was added, and the mixture was refluxed at 120°C for seven hours. The reaction liquid was discharged into iced water, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and TZ331 was obtained 72.5 mg (79 %).

TZ331: Yellow needles (methylene chloride/ n-hexane); mp 284°C;

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 8.31 (brs, 1H), 7.77 (s, 1H), 7.36 (d, J = 8.8Hz, 2H), 7.19 (s, 1H), 7.17 (s, 1H), 6.81 (d, J = 8.8Hz, 2H), 5.74 (s, 1H), 2.19 (s, 3H), 1.69 (s, 4H), 1.29 (s, 6H), 1.25 (s, 6H),  
Anal. Calcd. for C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S, C= 71.40%, H= 6.71%, N= 6.66 %.

#### Example 35: Synthesis of TZ333.



3-iodobenzoic acid methyl 1.77 g (6.77 mmol), Compound XIV-3, 1.47 g (6.77 mmol) and *tert*-BuONa 763mg (7.91 mmol) were dissolved in anhydrous toluene 15 ml, and, under argon replacement, tris (dibenzylideneacetone) dipalladium(0) 122 mg (0.14 mmol), (R)-BINAP 187mg

(0.30 mmol) were added, and the mixture was stirred at 100°C for two hours 30 minutes. The reaction liquid was cooled to room temperature, and extraction was carried out with ether. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 8) and Compound XV-1 was obtained 1.45 g (61 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 7.59 (t, J = 2.0Hz, 1H), 7.48 (td, J = 7.7, 1.2Hz, 1H), 7.27 (t, J = 7.8 Hz, 1H), 7.20 (s, 1H), 7.14 (s, 1H), 7.04 (m, 1H), 5.42 (brs, 1H), 3.88 (s, 3H), 2.19 (s, 3H), 1.68 (s, 4H), 1.29 (s, 6H), 1.24 (s, 6H).

Compound XV-1, 1.44 g (4.10 mmol) was dissolved in anhydrous benzene 16 ml, and acetyl chloride 386 mg (4.92 mmol), anhydrous pyridine 1 ml were added, and the mixture was stirred at room temperature for two hours. Acetyl chloride 0.20 ml was added to the reaction liquid and the liquid was further stirred at 50°C for four hours and further at 70°C for six hours. Iced water was added to the reaction liquid and extraction was carried out with ethyl acetate. The organic layer was washed with 2N hydrochloric acid and aqueous sodium chloride, it was dewatered with MgSO<sub>4</sub>, and thereafter, it was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and Compound XV-2 was obtained 1.37 g (85 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 8.00 (s, 1H), 7.82 (m, 1H), 7.45 (td, J = 8.0, 2.2Hz, 1H), 7.37 (bt, J = 8.3 Hz, 1H), 7.19 (brs, 1H), 7.15 (s, 1H), 3.88 (s, 3H), 2.10 (s, 3H), 1.96 (s, 3H), 1.69 (s, 4H), 1.27 (s, 12H).

Compound XV-2, 1.37 g (3.49 mmol) was dissolved in THF 8 mL under argon replacement, and DIBAL 10.5 mL (1M toluene solution, 10.5 mmol) was added slowly dropwise while stirring at -78°C. After 30 minutes, the reaction liquid was discharged into 2N hydrochloric acid, and extraction was carried out with ethyl acetate. The organic layer was washed with 2N hydrochloric acid and aqueous sodium chloride, and it was dewatered with MgSO<sub>4</sub>, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and Compound XV-3 was obtained 0.91 g (81 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 7.21 (t, J = 7.7Hz, 1H), 7.20 (s, 1H), 7.12 (s, 1H), 6.92 (s, 1H), 6.82 (m, 2H), 5.35 (brs, 1H), 4.62 (d, J = 5.8Hz, 2H), 2.19 (s, 3H), 1.68 (s, 4H), 1.59 (t, J = 5.8 Hz, 1H), 1.28 (s, 6H), 1.23 (s, 6H).

Compound XV-3, 900mg (2.79 mmol) was dissolved in methanol-free methylene chloride 12 ml, and active MnO<sub>2</sub> 2.86 g (85 %, 27.9 mmol) was added, and the mixture was stirred at room temperature for 15 hours. The reaction liquid was filtered, and the filtrate was concentrated, and thereafter, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 8) and Compound XV-4 was obtained 119 mg (13 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 9.92 (s, 1H), 7.37 (t, J = 7.7Hz, 1H), 7.31 (m, 2H), 7.18 (s, 1H), 7.15 (s, 1H), 7.09 (m, 1H), 5.48 (brs, 1H), 2.19 (s, 3H), 1.68 (s, 4H), 1.29 (s, 6H), 1.24 (s, 6H).

Compound XV-4, 115mg (0.36 mmol), 2,4-thiazolidinedione 84 mg (0.72 mmol) were suspended in anhydrous toluene 8 ml, and a solution of piperidine 9.2 mg (0.11 mmol) and acetic acid 6.4 mg (0.11 mmol) dissolved in anhydrous toluene 1.1 ml was added, and the mixture was refluxed at 120°C for seven hours. The reaction liquid was discharged into iced water, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and TZ333 was obtained 138 mg (92 %).

TZ333: Yellow needles (ethyl acetate / n-hexane); mp 223°C,

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 8.29 (brs, 1H), 7.75 (s, 1H), 7.30 (t, J = 8.1Hz, 1H), 7.17 (s, 1H), 7.15 (s, 1H), 6.93 (m, 2H), 6.81 (m, 1H), 5.43 (s, 1H), 2.19 (s, 3H), 1.69 (s, 4H), 1.30 (s, 6H), 1.24 (s, 6H),

Anal. Calcd. for C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S, C= 71.40%, H= 6.71%, N= 6.66%,

Found, C= 71.20%, H= 6.76%, N= 6.65%.

#### Example 36: Synthesis of TZ335.

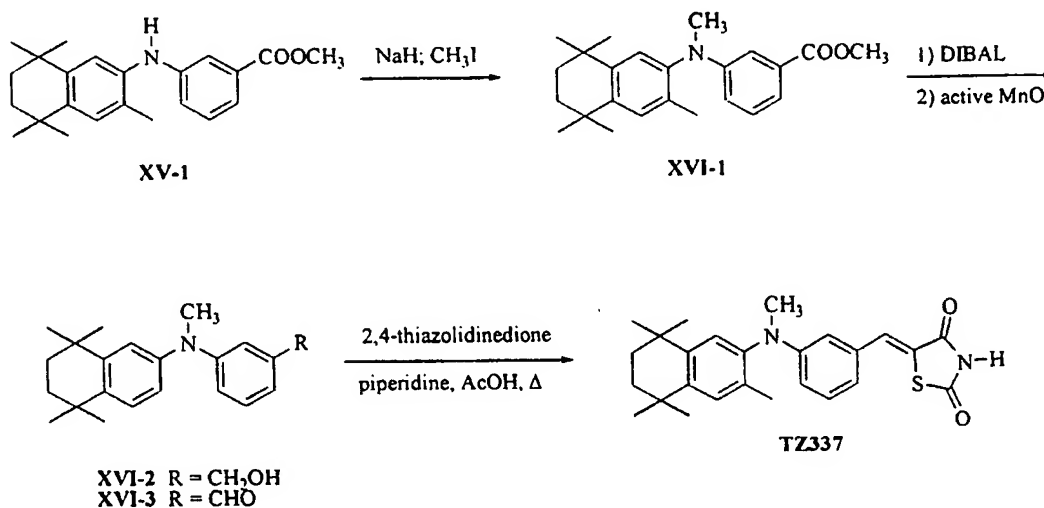
NaH 40mg (60 %, 1.01 mmol) was washed with little amount of n-hexane, and it was suspended in DMF 1 ml. XIV-7, 216mg (0.67 mmol) dissolved in 6 mL of DMF was added in this suspension, and the mixture was stirred at room temperature for 20 minutes. CH<sub>3</sub>I 0.08 mL (1.35 mmol) was added to the reaction liquid, and the mixture was stirred time for 30 minutes. DMF was distilled under reduced pressure and water was added and the mixture was extracted with methylene chloride. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 4) and XIV-8 was obtained 140 mg (62 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 9.73 (s, 1H), 7.67 (d, J = 8.1 Hz, 2H), 7.20 (s, 1H), 7.03 (s, 1H), 6.54 (brs, 2H), 3.30 (s, 3H), 2.04 (s, 3H), 1.69 (s, 4H), 1.31 (s, 6H), 1.23 (s, 6H).

XIV-8, 130mg (0.39 mmol), 2,4-thiazolidinedione 45 mg (0.39 mmol) were suspended in anhydrous toluene 6 ml, and a solution of piperidine 9.9 mg (0.12 mmol) and acetic acid 7 mg (0.12 mmol) dissolved in anhydrous toluene 1.2 ml was added, and the mixture was refluxed at 120°C. After six hours, the reaction liquid was discharged into iced water and extraction was carried out with methylene chloride. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and TZ335 was obtained 145 mg (86 %).

TZ335: Yellow powder (methylene chloride / methanol); mp >300°C,  
<sup>1</sup>H-NMR (400MHz, DMSO-d<sub>6</sub>, 30°C) 12.30 (brs, 1H), 7.63 (s, 1H), 7.39 (d, J = 8.4Hz, 2H), 7.29 (s, 1H), 7.09 (s, 1H), 6.53 (d, J = 8.3Hz, 2H), 3.29 (s, 3H), 1.99 (s, 3H), 1.65 (s, 4H), 1.27 (s, 6H), 1.21 (s, 6H),  
Anal. Calcd. for C<sub>26</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>S, C = 71.86%, H = 6.96%, N = 6.45%,  
Found, C = 71.60%, H = 6.99%, N = 6.67%.

**Example 37: Synthesis of TZ337.**



NaH 146mg (60 %, 3.65 mmol) was washed with little amount of n-hexane, and it was suspended in DMF 1 ml. XV-1, 855mg (2.44 mmol) was dissolved in 12 mL of DMF was added to this suspension, and the mixture was stirred at room temperature for 20 minutes. CH<sub>3</sub>I 0.30 ml (4.87 mmol) was added to the reaction liquid, and the mixture was stirred for one hour. DMF was distilled under reduced pressure, water was added and the mixture was extracted with methylene chloride. The organic layer was washed with aqueous sodium chloride, and was dewatered with MgSO<sub>4</sub>, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 10) and XVI-1 was obtained 788.5 mg (89 %).

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>) 7.34 (d, J = 7.7Hz, 1H), 7.30 (m, 1H), 7.17 (s, 1H), 7.16 (t, J = 7.7Hz, 1H), 7.04 (s, 1H), 6.59 (dd, J = 7.4, 1.8 Hz, 1H), 3.88 (s, 3H), 3.25 (s, 3H), 2.04 (s, 3H), 1.68 (s, 4H), 1.30 (s, 3H), 1.22 (s, 3H).

XVI-1, 750mg (2.05 mmol) was dissolved in THF 7 mL under argon replacement, and DIBAL 6.16 mL (1M toluene solution, 6.16 mmol) was added dropwise gradually while stirring at -78°C. After 30 minutes, the reaction liquid was discharged into 2N hydrochloric acid, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and

was dewatered with  $\text{MgSO}_4$ , and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and XVI-2 was obtained 616 mg (89 %).

$^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ) 7.16 (s, 1H), 7.14 (t, J = 7.7Hz, 1H), 7.04 (s, 1H), 6.68 (d, J = 7.3Hz, 1H), 6.58 (s, 1H), 6.41 (dd, J = 8.1, 2.2Hz, 1H), 4.60 (d, J = 5.8Hz, 2H), 3.22 (s, 3H), 2.06 (s, 3H), 1.68 (s, 4H), 1.52 (t, J = 5.9 Hz, 1H), 1.30 (s, 6H), 1.21 (s, 6H).

XVI-2, 610mg (1.81 mmol) was dissolved in methanol-free methylene chloride 8 ml, and active  $\text{MnO}_2$  1.85g (85 %, 18.1 mmol) was added, and the mixture was stirred at room temperature for 30 hours. The reaction liquid was filtered, the filtrate was concentrated, and thereafter, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 10) and XV-3 was obtained 423 mg (70 %).

$^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ) 9.91 (s, 1H), 7.28 (t, J = 7.3Hz, 1H), 7.18 (m, 2H), 7.07 (m, 1H), 7.04 (s, 1H), 6.69 (dd, J = 8.4, 2.6Hz, 1H), 3.26 (s, 3H), 2.05 (s, 3H), 1.69 (s, 4H), 1.31 (s, 6H), 1.22 (s, 6H).

XV-3, 415mg (1.24 mmol), 2,4-thiazolidinedione 145 mg (1.42 mmol) were suspended in anhydrous toluene 10 ml, and a solution of piperidine 32 mg (0.37 mmol) and acetic acid 22 mg (0.37 mmol) dissolved in anhydrous toluene 4 ml was added, and it was refluxed at 120°C. Six hours were allowed to pass, and the reaction liquid was discharged into iced water and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with  $\text{MgSO}_4$ , and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and TZ337 was obtained 504 mg (94 %).

TZ337: Orange crystals (ethyl acetate / n-hexane); mp 219°C

$^1\text{H-NMR}$  (400MHz,  $\text{CDCl}_3$ ) 8.22 (brs, 1H), 7.74 (s, 1H), 7.27 (t, J = 7.7Hz, 1H), 7.04 (s, 1H), 6.80 (d, J = 8.4Hz, 1H), 6.64 (dd, J = 8.0, 2.2Hz, 1H), 6.48 (s, 1H), 3.26 (s, 3H), 2.05 (s, 3H), 1.70 (s, 4H), 1.32 (s, 6H), 1.24 (s, 6H),

Anal. Calcd. for  $\text{C}_{26}\text{H}_{30}\text{N}_2\text{O}_2\text{S}$ , C= 71.86%, H= 6.96%, N= 6.45%;

Found, C= 71.65%, H= 7.16%, N= 6.75%.

#### Example 38: Test Example.

Using each compound of this invention, effect with respect to cell differentiation induction action when alone and cell differentiation induction action when retinoid was also present were examined. Am80 [4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl) carbamoyl] benzoic acid was used as retinoid which was also present to make comparison. Using promyelocytic leukemia cell strain HL-60, differentiation to granulocyte system was assessed by change of form and measured by ability to reduce nitroblue tetrazolium (NBT). The proportion of cells which had differentiated (%) as shown in the following table is calculated from the ability to reduce NBT.

(A) The concentration-dependence of the ability to induce differentiation inducibility of each compound individually and the concentration-dependent effect of  $1 \times 10^{-9}$  M Am80 was measured. TZ91 and TZ181 showed cell differentiation induction activity even alone, and furthermore, the activity of Am80, which was also present in a concentration where it did not exhibit cell differentiation induction activity, was strengthened. Moreover, TZ201 did not have activity on its own, but inhibited the activity of Am80 which is also present.

**Table 1**

	Proportion (%) of differentiated cells with compound alone				Proportion (%) of differentiated cells with $1 \times 10^{-9}$ M Am80 also present				
Com- pound	concentration				concentration				
	-9	-8	-7	-6	None	-9	-8	-7	-6
TZ91	1.2	0.8	7	87	49	58	62	87	-
TZ181	-	1	7	54	37	-	53	58	6
TZ201	-	0.3	0.7	0.3	48	-	64	53	5

(B) Concentration-dependent differentiation inducibility with respect to each compound alone and concentration-dependent differentiation inducibility in the presence of  $1 \times 10^{-10}$  M Am80 was measured. TZ151 showed cell differentiation induction activity alone, and when Am80 was also present at a concentration at which it did not show cell differentiation induction activity, the activity was enhanced further. Moreover, neither TZ161 nor TZ191 have activity alone, but enhanced the activity of Am80 which was also present, and acted in an inhibitory manner at high concentration ( $1 \times 10^{-6}$  M).

**Table 2**

	Proportion (%) of differentiated cells with compound alone			Proportion (%) of differentiated cells with $1 \times 10^{-10}$ M Am80 also present			
Compound	concentration			concentration			
	-8	-7	-6	None	-8	-7	-6
TZ151	3	4.4	78	4	12	43	83
TZ161	3.5	1.8	3.6	4	12	25	3.8
TZ191	3.6	3.5	4.1	11	63	75	28

(C) Concentration-dependent differentiation inducibility with respect to each compound alone and concentration-dependent differentiation inducibility in the presence of  $3 \times 10^{-9}$  M Am80 was measured. All the aforesaid 5 compounds other than TZ241 showed cell differentiation induction activity alone, and when Am80 was also present at a concentration at which it did not show cell differentiation induction activity, further enhanced activity was observed for all 5 compounds.

Table 3

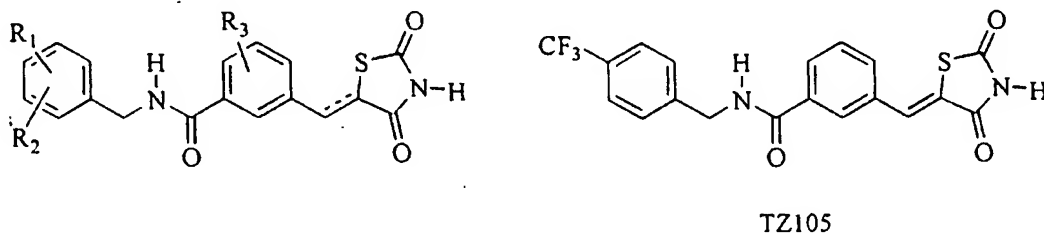
	Proportion (%) of differentiated cells with compound alone			Proportion (%) of differentiated cells with $1 \times 10^{-9}$ M Am80 also present			
Compound	concentration			concentration			
	-8	-7	-6	none	-8	-7	-6
TZ221	1.4	2	51	44	54	67	82
TZ241	2.8	6.4	89	44	76	84	92
TZ245	3.8	3	11	44	86	89	88
TZ321	1.2	1.1	28	51	55	83	88
TZ325	2.2	21	87	51	72	83	79

(D) Concentration of each compound was fixed at  $1 \times 10^{-6}$ M, and effect with respect to concentration-dependent differentiation inducibility of retinoid (Am80) was measured. The aforesaid 4 compounds did not exhibit cell differentiation induction activity alone, and inhibited the activity of Am80 which was also present.

Table 4.

Compound	Retinoid also present (concentration)			
	none	Am80(-9)	Am80(-9.5)	Am80(-10)
none	1.5	80	53	8.5
TZ223	4.4	62	22	5
TZ227	5.3	11.7	5.5	7
TZ243	4.2	77	35	5
TZ247	7	10	5.8	6.4

(E) In Kokai 9-48771, it is demonstrated that N-benzyl dioxo thiazolidyl benzamide derivatives represented by following general formula have insulin resistance improvement action. Therefore, TZ105 was synthesised as an N-benzyl derivative for comparison, and examined for presence or absence of retinoid activity.



II-2 (Example 4) 150 mg (0.60 mmol) was suspended in anhydrous benzene 12 ml, and  $\text{SOCl}_2$  358mg (3.01 mmol) was added, and the mixture was refluxed for 14 hours. The  $\text{SOCl}_2$  was eliminated by distillation, and thereafter the residue was suspended in anhydrous benzene 10 ml, and 4-trifluoro benzylamine 106 mg (0.60 mmol), anhydrous pyridine 1 ml were added, and the mixture was stirred at room temperature for one hour. To the reaction liquid was added 2N hydrochloric acid with ice floating, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and water was removed with  $\text{MgSO}_4$ , and thereafter, it was concentrated, and thereafter, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 3 : 2) and TZ105 was obtained 128 mg (52 %).

TZ105: Colorless needles (ethyl acetate /n-hexane); mp 204°C,  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ , 30°C ) 9.23 (t, 1H, J = 5.9 Hz), 8.10 (s, 1H), 7.97 (d, 1H, J = 8.7 Hz), 7.83 (s, 1H), 7.76 (d, 1H, J = 8.7 Hz), 7.70 (d, 2H, J = 8.1 Hz), 7.65 (t, 1H, J = 7.7 Hz), 7.55 (d, 2H, J = 8.0 Hz), 4.59 (d, 2H, J = 5.9 Hz); Anal. Calcd. for  $\text{C}_{19}\text{H}_{13}\text{N}_2\text{O}_3\text{SF}_3$ , C: 56.16%, H: 3.22%, N: 6.89%, Found C: 56.36%, H: 3.04%, N: 6.98 %.

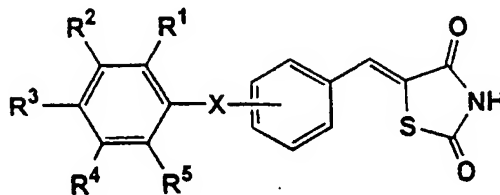
In assay system using HL-60 cell described above, TZ105 did not exhibit any differentiation induction activity at all, and also it did not exert any influence on the action of retinoid Am80 which was also present. Accordingly, retinoid or retinoid inhibition action is not displayed by the N-benzyl compound, and it is thought that in this structure, it is essential that a nitrogen atom is present in the aromatic ring, as in TZ185 and the like.

#### Possible Applications in Industry

Because the compounds of this invention display a retinoid-like activity or retinoid-like activity regulation by acting on retinoid receptor, (enhancement or inhibition of retinoid action), they are useful as effective ingredient of drug for prevention and/or therapy of disease such as cancer, diabetes mellitus, arteriosclerosis, bone disease, rheumatism or immunologic disease or the like.

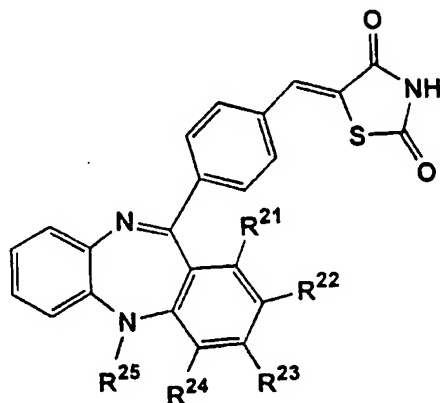
### Patent Claims

1. A compound represented by the following general formula (I)



(wherein, R1, R2, R3, R4 and R5 each independently denote hydrogen atom or lower alkyl group, and among these, two adjacent groups, together with carbon atoms of phenyl ring that they are bonded to, may bond to form a 5-membered ring or 6-membered ring optionally having 1 or more alkyl groups; X denotes a group represented by -C(R6)=CH-, -CH=C(R7)-, -N(R8)-CO-, -CO-N(R9)-, -C(=CHR10), -CO- or -NR11- (wherein, R6, R7, R8, R9, R10 and R11 each independently denote hydrogen atom or lower alkyl group)), or

a compound represented by following general formula (II)



(wherein, R21, R22, R23 and R24 each independently denote hydrogen atom or lower alkyl group, and among these, two adjacent groups, together with carbon atoms of phenyl ring that they are bonded to, may bond to form a 5-membered ring or 6-membered ring optionally having 1 or more alkyl groups; and R25 denotes a hydrogen atom or lower alkyl group) or salts thereof.

2. The drug which includes, as active component, a substance selected from the group comprising compound of formula (I) or formula (II) in accordance with Claim 1, and physiologically acceptable salts thereof, and hydrates and solvates thereof.

3. A drug in accordance with Claim 2 which is retinoid receptor agonist.

4. A drug in accordance with Claim 2 or 3 having action to enhance the action of retinoid.
5. A regulator in accordance with Claim 2 or 3 having action to inhibit the action of retinoid.

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